Synthetic Studies on Molecules Related to the Azinothricin Family and Allopumiliotoxin 339A

A Thesis Presented to the University of London
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for the Degree of Doctor of Philosophy

Amandine Andrée Huguette LEFRANC

Christopher Ingold Laboratories
Department of Chemistry
University College London
London WC1H 0AJ

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ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
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ABSTRACT

The Azinothricin family of compounds are based on a cyclodepsipeptide core and were first encountered in the late 1980s. Most of the members exhibit potent antitumour and antibiotic activities. In 1997, the Hale group synthesised A83586C through a chemoselective coupling strategy between an unprotected cyclohexadepsipeptide and a fully elaborated pyran activated ester. In this thesis, the asymmetric synthesis of two cyclodepsipeptides analogues are investigated, the L-proline analogue of GE3 cyclodepsipeptide and the (3*S*,5*S*)-5-hydroxypiperazic acid analogue of A83586C cyclodepsipeptide. The synthesis of analogues may be of value for elucidating the mode of action of these natural products. Furthermore, it might allow the identification of a considerably simplified structure for industrial purposes.

In a second project, a new approach to the synthesis of (+)-allopumiliotoxin 339A was studied. The pumiliotoxin and allopumiliotoxin class of amphibian alkaloids displays significant cardiotonic activity. Allopumiliotoxin 339A is one of the most potent compounds of the family; its activity is due to an interaction with a modulatory site on the voltage-dependent sodium channel. Our strategy to (+)-allopumiliotoxin 339A was based on the synthesis of two main fragments, an α-alkoxyaldehyde and a functionalised side chain fragment. Our initial research to the α-alkoxyaldehyde involved a Sharpless Asymmetric Aminohydroxylation reaction. However, this reaction proved not to be feasible on the trisubstituted alkene precursor. Eventually the α-alkoxyaldehyde was successfully prepared using a Trost's opening of an epoxide followed by an asymmetric induction of chiral sulfinimine to access the desired stereochemistry. The synthesis of the side chain segment was achieved via an *O*-directed hydrostannation strategy developed in the Hale group. This strategy allowed the stereoselective synthesis of the trisubstituted alkene moiety of the side chain.

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I wish to thank Julien for helping me get through the difficult times, and for all the emotional support he provided.

I cannot end without thanking my family, especially my parents, on whose constant encouragement and love I have relied throughout my time at UCL.

ABBREVIATIONS

Ac	acetyl
acac	acetylacetonate
AIBN	azobisisobutyronitrile
All	allyl
Ar	aryl
B^-	base
BAIB	[bis(acetoxy)iodo]benzene
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOM	benzyloxymethyl
BOP reagent	benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate
BOPCl	*N*-*N*-bis(2-oxo-3-oxazolidinyl)phosphinic chloride
br	broad
n-Bu	*n*-butyl
t-Bu	*t*-butyl
Bz	benzoyl
CI	chemical ionisation
m-CPBA	*meta*-chloroperbenzoic acid
CSA	camphorsulfonic acid
d	doublet
dd	doublet of doublet
ddd	doublet of doublet of doublet
dt	doublet of triplet
dba	dibenzilideneacetone
DBAD	di-*tert*-butylazodicarboxylate
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	1-2-dicyclohexylcarbodiimide

DCM	dichloromethane
DDQ	dichlorodicyanoquinone
DEPC	diethylphosphorocyanidate
$(DHQD)_2PHAL$	1,4-bis(9-*O*-dihydroquinidinyl)-phthalazine
$(DHQ)_2PHAL$	1,4-bis(9-*O*-dihydroquininyl)-phthalazine
DIEA	*N,N*-diisopropylethylamine (Hünig's base)
DIBAL-H	diisobutylaluminium hydride
DMAP	4-(dimethylamino)pyridine
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMPU	1,3-dimethyl-3-4-5-6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethylsulfoxide
DNP	dinitrophenyl
dppf	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereoisomeric ratio
E^+	electrophile
ee	enantiomeric excess
ESI	electrospray ionisation
eq	equivalent
Et	ethyl
FAB	fast atomic bombardment
Fmoc	fluorenylmethyloxycarbonyl
h	hour
HATU	*N*-[(dimethylamino)-1*H*-1,2,3-triazolo[4,5,*b*]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate
HOBt	1-hydroxybenzotriazole
HMBC	heteronuclear multiple bond connectivity
HMPA	hexamethylphosphoramide
HMQC	heteronuclear multiple quantum coherence
HRMS	high resolution mass spectroscopy

Hz	Hertz
IR	infra red
J	coupling constant
KHMDS	potassium hexamethyldisilazide
L	ligand
LDA	lithium diisopropylamide
LiDBB	lithium di-*tert*-butylbiphenyl
m	*meta*
M	molar
m/z	mass to charge ratio
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
min	minute
mM	milimolar
MOM	methoxymethyl
Ms	methylsulfonyl
MS	molecular sieves
MTPA	methoxy(trifluoromethyl)phenylacetyl)
NBS	*N*-bromosuccinimide
NEM	*N*-ethylmorpholine
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
Nu^-	nucleophile
o	*ortho*
ox.	oxidation
p	*para*
PCC	pyridinium chlorochromate
PG	protecting group
Ph	phenyl
Piz	piperazic

PMB	*para*-methoxybenzyl
PPTS	pyridinium *para*-toluenesulfonate
i-Pr	isopropyl
PTX	pumiliotoxin
pyr	pyridine
R	alkyl
RedAl-H	sodium bis(2-methoxyethoxy)aluminum hydride
rt	room temperature
s	singlet
SAA	Sharpless Asymmetric Aminohydroxylation
SEM	[2-(trimethylsilyl)ethoxy]methyl
SM	starting material
t	triplet
TBAF	tetra *n*-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetamide
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetra-*n*-propylammonium perruthenate
Troc	trichloroethoxycarbonyl
Ts	*p*-toluenesulfonyl
Z	benzyloxycarbonyl

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PART A: SYNTHETIC STUDIES ON MOLECULES RELATED TO THE AZINOTHRICIN FAMILY

In recent years, interest in phamacologically active natural products has occupied a central position in organic chemistry. Cyclodepsipeptides are cyclic peptides possessing at least one ester linkage and their chemical syntheses represent a considerable challenge. Indeed, their unusual architecture stimulated many synthetic chemists leading them to develop numerous new synthetic methodologies. These molecules also exhibit potent biological activities. Thus, the chemical synthesis of cyclodepsipeptides can provide leads for the development of novel pharmaceutical agents.

1. The Azinothricin family of antibiotics

1.1. Biological introduction

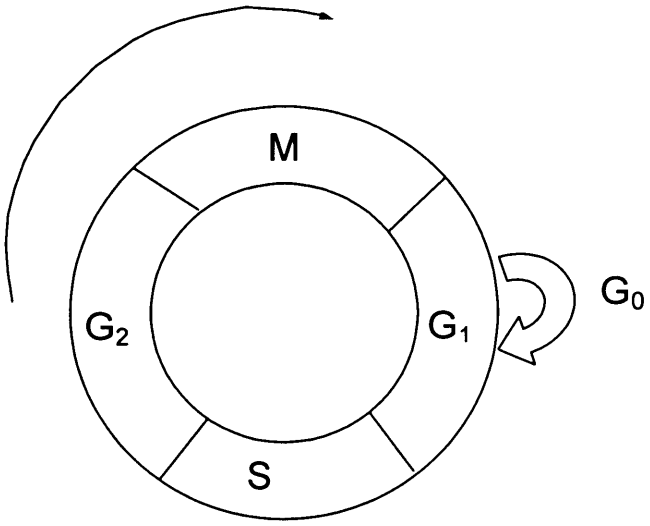


Figure 1. The cell cycle

To understand the basis of cancer biology, it is necessary to understand the mechanisms that control cell growth and cell cycle. In fact, most eukaryotic cells reproduce

through a sequence of four phases: 2 gap phases (G_1 and G_2) where RNA and protein are synthesised, one synthesis phase (S) where DNA synthesis or replication occurs, and mitosis (M), in which the cell's chromosomes are divided between two daughter cells. The cell can also temporarily or reversibly exit cell cycle and enter a state of quiescence called G_0 phase. A molecular surveillance system monitors the progress of cell cycle through various check points of which the two most important are between G_1 and S and between G_2 and M. Proto-oncogenes are genes which promote cell growth and mitosis, and tumor suppressor genes discourage cell growth, or temporarily halt cell division in order to carry out DNA repair. Typically, a series of several mutations to these genes are required before a normal cell transforms into a cancer cell. E2F transcription factors[1-4] regulate the expression of genes that control cell proliferation during the G_1/S transition. The mechanisms of action of E2Fs are very complex, and involve a network of interactions with various molecules. A pathway in which E2F is regulated by its interaction with the retinoblastoma protein (pRB), a tumor suppressor protein, had been identified.[5] It is known that virtually all human cancers exhibit alterations in this pRb/E2F pathway.[6] In this regard, targeting E2Fs could be a promising approach to treat cancer and molecules of the Azinothricin family that are known to inhibit, directly or indirectly, E2F transcription factors might serve as antiproliferative drugs.

1.2. Isolation and Biological Activity of Some Member of the Family

In 1986, Maehr and co-workers at Hoffman La-Roche isolated the first member of a growing family of antitumour antibiotics from *Streptomyces sp. X14950.* [7] They named the new molecule azinothricin **1** and found it to be one of the most potent antibiotics ever discovered in the Roche natural product screening assay. Its MIC values[†] ranged from 0.008 to 0.063 µg/mL against a variety of Gram-positive strains of bacteria. The structure of azinothricin **1** is presented in Figure 2 along with other members of the family. It was determined by X-ray crystallography and chemical degradation.

[†] Minimum Inhibitory Concentration: the lowest concentration of drugs that prevents visible bacterial growth

Two years later, the second member of this family was discovered by Smitka *et al.*[8] It was named A83586C **2** and was isolated from fermentation broths of the Guam soil microorganism *Streptomyces Karnatakensis*. A83586C was highly toxic to mice at doses of 9.3 mg/kg and so its clinical development was never considered viable. However, it exhibited pronounced antitumour properties *in vitro* against a large number of cancer cells; it was particularly efficient at inhibiting growth of a CCRF-CEM human T-cell leukaemia line, its IC_{50}[‡] value being 0.0135 µg/ml. Recent work has shown that A83586C **2** exhibits activity against various other mouse and human tumour cell line HCT-116 human colon cancer cells (IC_{50} = 40 ± 10 nm), HT-29 cancer cells (IC_{50} = 60 ± 30 nm), MDA-MB-435 cancer cells (IC_{50} = 90 ± 10 nm), MCF-7 human breast cancer cells (IC_{50} = 90 ± 30 nm), A549 human lung cancer cells (IC_{50} = 30 ± 10 nm), PC-3M human prostate cancer cells (IC_{50} =160 ± 30 nm) and U2OS human ulterine cancer cells (IC_{50} = 80 ± 10 nm). A83586C **2** also possesses strong antibiotic properties against Gram-positive bacteria such as *Staphylococcus aureus*, *Staphylococcus epidermis*, *Streptococcus pyogenes*, and *Streptococcus pneumoniae*.

Other isolated molecules of this class include citropeptin[9] **3** in 1990, GE3[10,11] **4** in 1997, and Kettapeptin[12] **5** in 2006 (Figure 2).

‡ Inhibitory Concentration: Concentration of a drug required to observe 50% inhibition of tumour growth

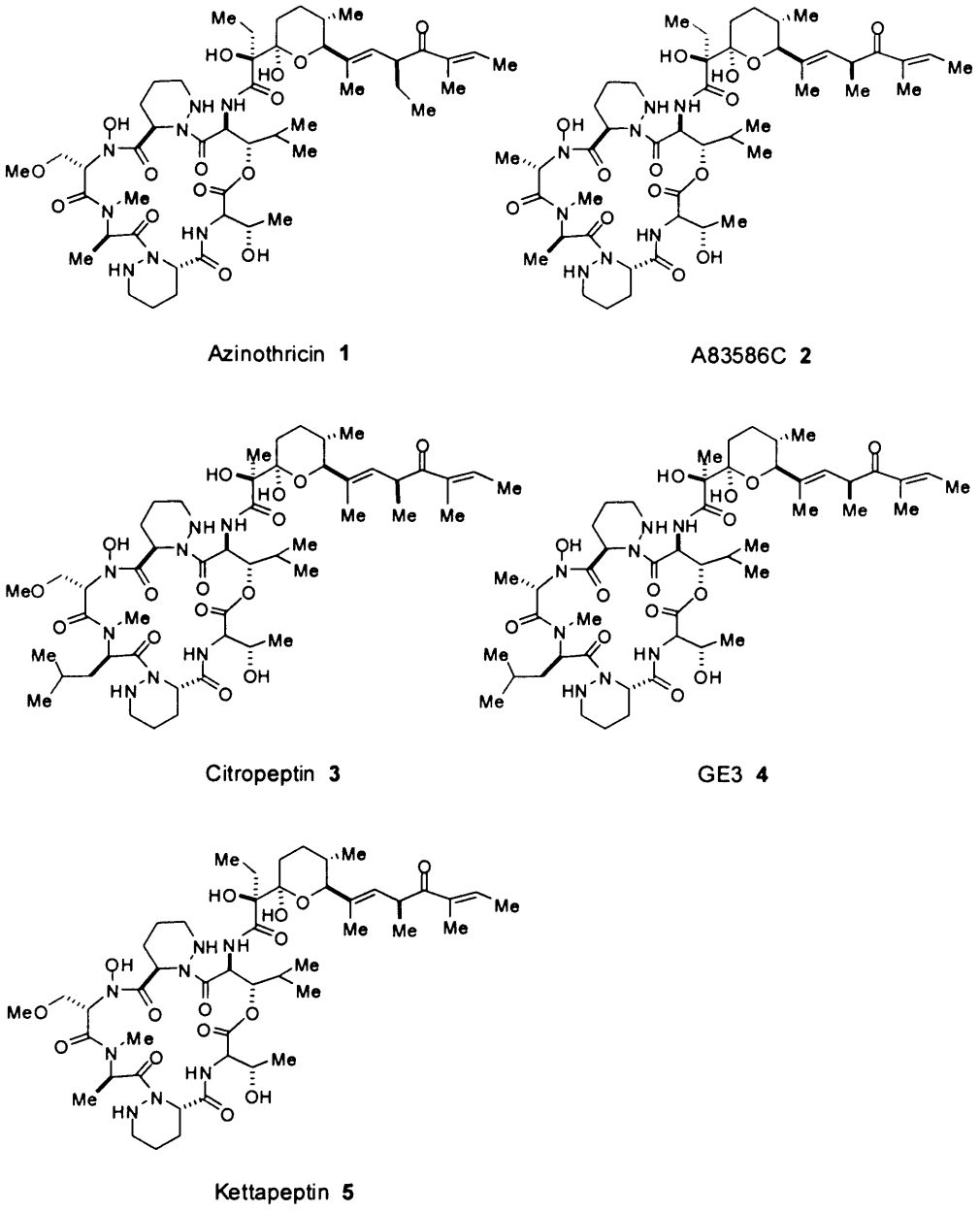


Figure 2. Structure of the A83586C/Azinothricin Family of Antibiotics

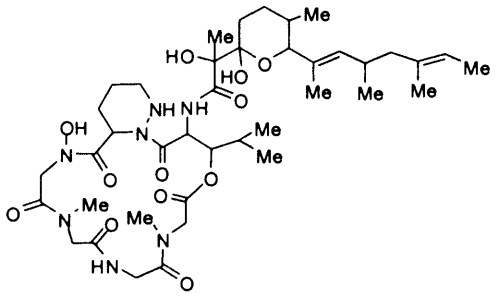
Citropeptin **3** shows *in vitro* and *in vivo* activity against P388 leukaemia cells. Its IC_{50} value is 0.02 μg/mL and it provides 120% life extension when given to mice with P388 lymphocytic leukaemia at the non-toxic dose of 2 mg/kg/day.

The producing strain GE3 **4** was isolated from a soil sample collected in Shimane prefecture, Japan. GE3 **4** possesses antibacterial and antitumour activities against human pancreatic carcinoma, PSN-1 both *in vitro* and *in vivo*. It exhibits high *in vitro* cytoxicity against human tumour cell lines HeLa S3, A431 and Saos-2 with IC_{50} value of 6nM, 16 nM, and 3.6 nM

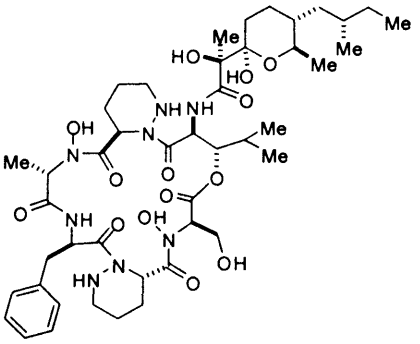
respectively. The *in vivo* activity was examined in the human xenograft mouse tumour model: a 47% reduction in tumour size was observed when GE3 **4** was given to mice at the non-toxic dose of 2 mg/kg/day. Contrary to A83586C **2**, it showed only a weak activity against Gram-positive strains of bacteria. It is noteworthy that only two structural diffferences between GE3 **4** and A83586C **2** are responsible for divergent profiles against bacteria.

More recently, Kettapeptin **5** was isolated by Maskey and co-workers from the ethyl acetate extract of the *Streptomyces sp.* Isolate GW99/1572.[12] It exhibits antibacterial activity against *Bacillus subtilis* with a MIC value of 3.75 µg/mL, and also against *Streptomyces viridochromogenes*, *Staphylococcus aureus* and *Escherichia coli.* Furthermore, Kettapeptin **5** shows anticancer activity against human cell lines LXFA 629L, LXFL 529L, MAXF 401NL, MEXF 462NL, RXF944L and UXF 1138L with IC_{50} values of < 0.6 µg/mL.

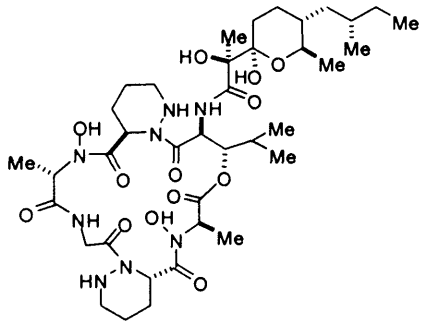
Other cyclodepsipeptides that are considered to belong to the Azinothricin family include the molecules shown in Figure 3: Verucopeptin **6**,[13,14] Variapeptin **7**,[9] L-156,602 **8**[15] and Polyoxypeptins A, **9** and B **10**,[16] IC101 **11**,[17] and the recently discovered Pipalamycin **12**.[18]



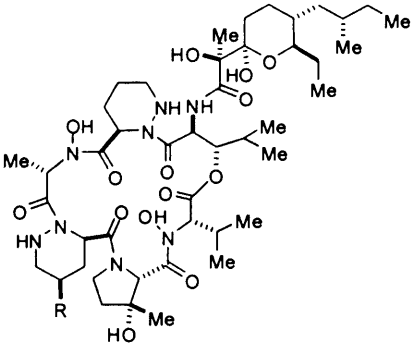
Verucopeptin **6**



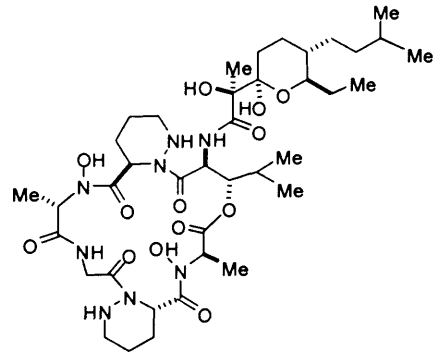
Variapeptin **7**



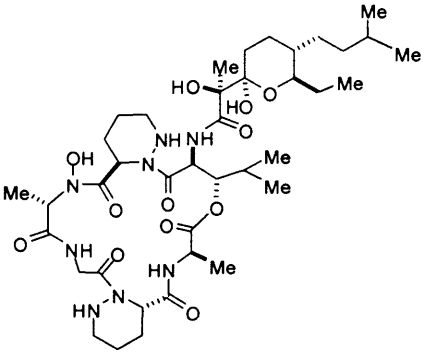
L-156,602 **8**



9 Polyoxypeptin A : R = OH
10 Polyoxypeptin B : R = H



IC101 **11**



Pipalamycin **12**

Figure 3.

Verucopeptin **6** was isolated in 1993 from the soil microorganism *Actinomadura verrucospora*, and exhibits specific *in vitro* toxicity against mouse B16-F10 cells with IC_{50} value of 0.004 µg/mL. Verucopeptin presents a weaker activity against P388 leukaemia and HCT-116 Human Colon Cancer with IC_{50} value of 0.08 µg/mL and 0.04 µg/mL respectively. *In vivo* activity was tested in the experimental mouse tumor system; Verucopeptin **6** significantly prolongs the

life expectancy of mice with B16 melanoma, conferring a 162% life extension when given at the dosage of 2 mg/kg/day.

Variapeptin **7**, was isolated from *Streptomyces variabilis,* that was taken from a soil sample collected in Bosque, Brazil. It showed a potent activity *in vitro* against Gram-positive strains of bacteria and demonstrated potent cytotoxicity against P388 leukaemia cells (IC_{50} = 0.01 μg/mL).

L-156,602 **8**, isolated from cultures of *Streptomyces* spp. MA6348, was found to be a C5a antagonist. Such molecules might function as anti-inflammatory agents or be useful for treating allergic disease states. Its total synthesis was achieved in 1990 by Durette *et al.*[19]

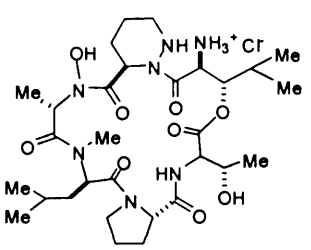
Polyoxypeptin A, **9** and polyoxypeptin B **10** were isolated in 1999 by Umezawa and coworkers[16] from the culture broth of *Streptomyces* MK498-98F14 and are known to exhibit potent apoptosis against human pancreatic adenocarcinoma AsPC-1 cells, an apoptosis-resistant cell line. Polyoxypeptins A, **9** and B, **10** decreased the viability in AsPC-1 cells with ED_{50} values of 0.08 and 0.17 μg/mL.

IC101 **11**[17,20] and Pipalamycin **12**[18] were isolated from the same strain; the producing strain, MJ202-73F3, was extracted with EtOAc, concentrated to dryness and purified by chromatography with $CHCl_3$/MeOH (50:1). IC101 **11** was eluted first as the major compound followed by Pipalamycin. IC101 inhibited MLCR (Mixed Lymphocyte Culture Response) with an IC_{50} value of 0.009 μg/mL and showed its strongest activity against $P388D_1$ cells (IC_{50} = 0.006 μg/mL). Pipalamycin **12** induced apoptosis in human pancreatic adenocarcinoma AsPC-1 cells at 0.3 μg/mL in 24-48 hours.

Almost all molecules of the cyclic hexadepsipeptide class have been found to show potent cytotoxicity. However mechanisms for cytotoxicity have been little described. The synthesis of analogues following by the comparison of their biological activities should give a

path to determine these mechanisms. Additionally, it might prove possible to find analogues that will possess interesting biological properties.

In this first part of my PhD, I worked on the synthesis of two modified cyclodepsipeptide analogues shown in Figure 4: the L-proline modified mimetic of GE3 cyclodepsipeptide **13** and the (3*S*, 5*S*)-5-hydroxypiperazic acid modified mimetic of A83586C cyclodepsipeptide **14**.



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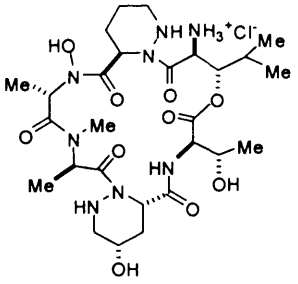
L-proline modified mimetic of GE3 cyclodepsipeptide



14

(3*S*, 5*S*)-5-hydroxypiperazic acid modified mimetic of A83586C cyclodepsipeptide

Figure 4. Two cyclodepsipeptide analogues

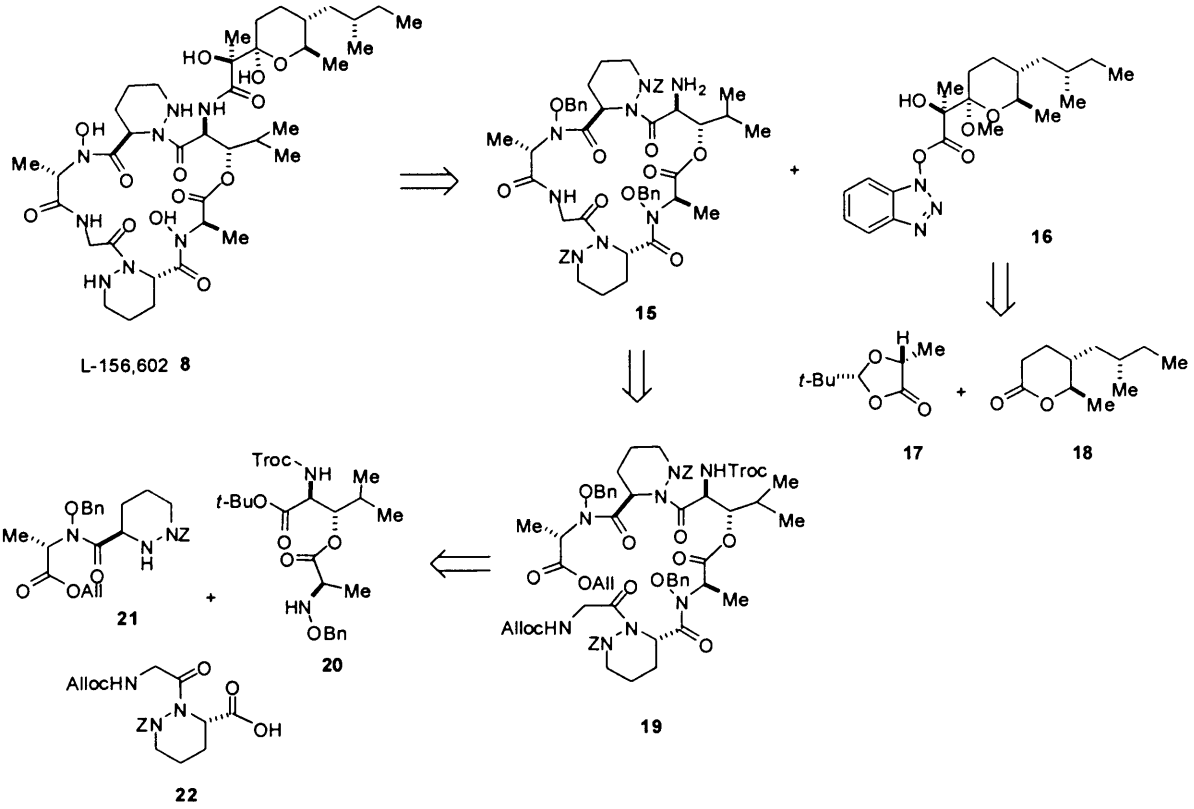
2. Previous work on the Azinothricin Family

Prior to our group's research, only one group has achieved a total synthesis of a molecule of the Azinothricin family. In this part, the synthesis of L-152,602 by Durette and coworkers will be reviewed along with the work published by our group on the Azinothricin family. This work includes the total synthesis of A83586C and the synthesis of the verucopeptin and GE3 cyclodepsipeptides. Additionally, two cyclodepsipeptides analogues were also prepared.

2.1. Past Syntheses of Some Related Natural Products

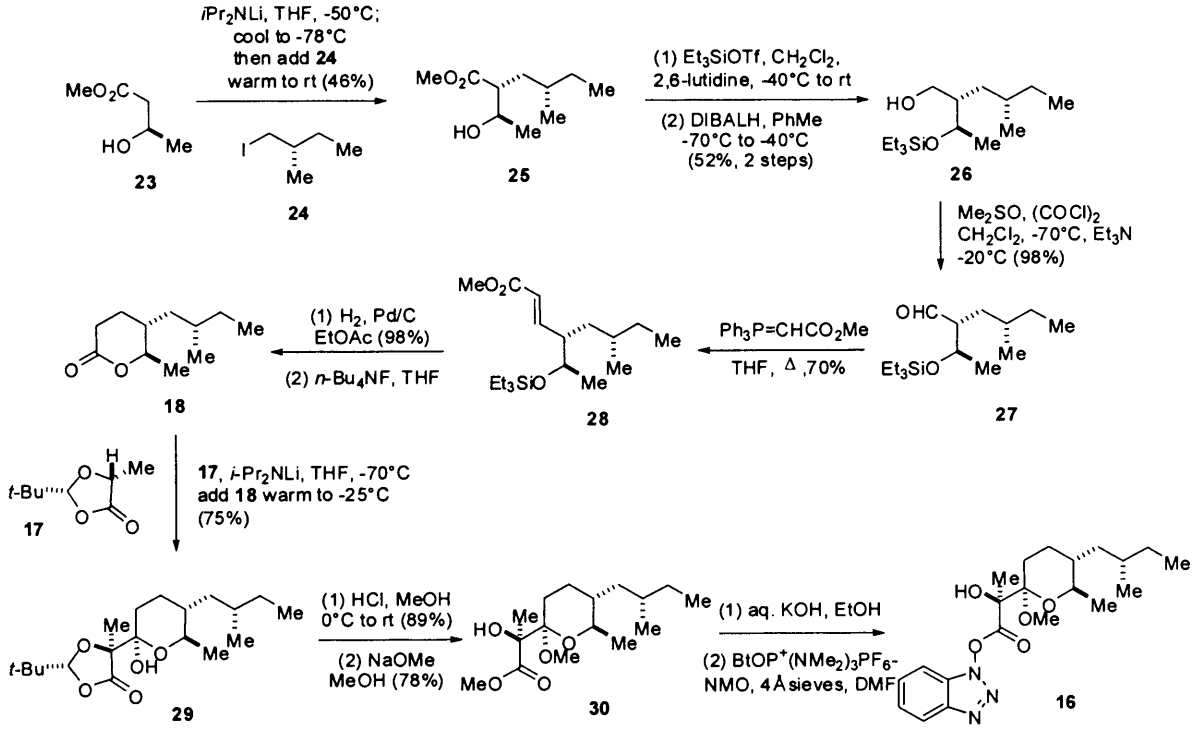
2.1.1. Total Synthesis of L-152,602

Durette and coworkers achieved the first total synthesis of L-152,602 **8** in 1990[19]. Their original plan was to complete the synthesis with a coupling between cyclodepsipeptide **15** and the HOBt activated ester **16** (Scheme 1). Activated ester **16** would be accessed *via* a Seebach enantioselective Claisen condensation reaction.[21] Cyclodepsipeptide **15** would originate from the linear hexapeptide **19**. The linkage selected to achieve the ring closure was the bond between the glycine and *N*-benzyloxy-L-alanine residues. The assembly strategy for hexapeptide **19** employed a [2 + 2 + 2] fragment condensation of dipeptides **20**, **21** and **22**.



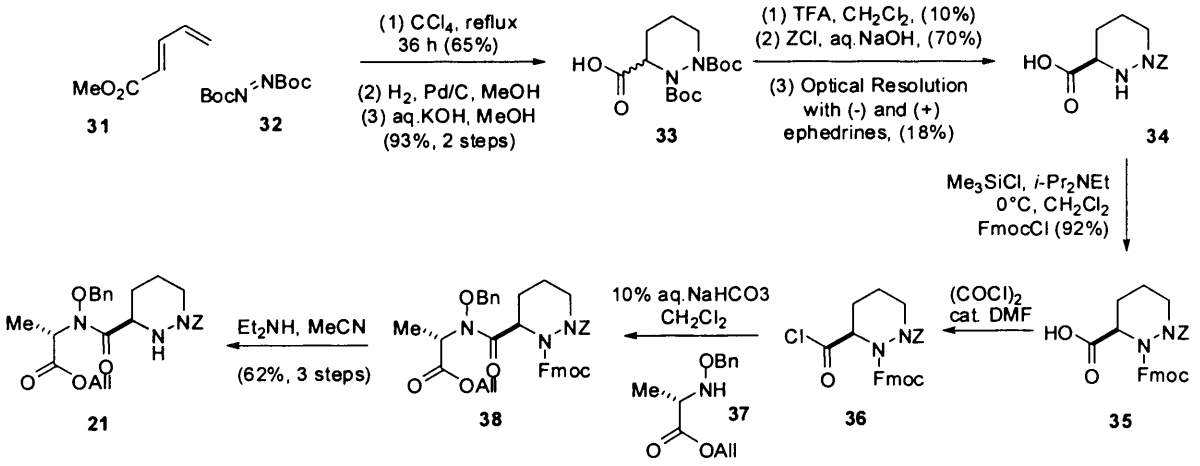
Scheme 1. Retrosynthetic plan to L-156,602 **8**

The synthesis of ester **16** started with a diastereoselective Frater-Seebach alkylation reaction of the enolate derived from methyl (*R*)-3-hydroxybutanoate **23** with (*S*)-1-iodo-2-methylbutane **24** to afford alcohol **25** in 46% yield. Subsequent protection of the hydroxyl group and reduction of the methyl ester gave alcohol **26** in 52% yield. After Swern oxidation, the product aldehyde **27** was condensed with carboxymethylphosphorane to give (*E*)-olefin **28** in 70% yield. Hydrogenation over Pd/C and *O*-desilylation led to concomitant ring closure affording lactone **18**. After a diastereoselective Claisen condensation between lactone **18** and the lithium enolate derived from dioxolane **17**, compound **29** was obtained as a single isomer in 75% yield. Compound **29** was then converted into the methyl pyranoside by treatment with methanolic HCl in 89% yield. Transesterification with excess sodium methoxide afforded methyl ester **30** which was converted into a potassium salt using potassium hydroxide. Finally, the *N*-hydroxybenzotriazole active ester **16** was prepared by reaction with the BOP reagent and NMO in DMF.



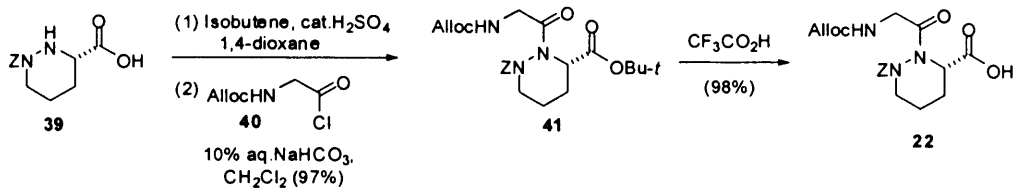
Scheme 2. Synthetic route to activated ester **16**

The synthesis of fragments **21** and **22** required the preparation of Z-protected piperazic acids **34** (3*R*) and **39** (3*S*). It was achieved *via* a Diels-Alder cycloaddition between 2,4-pentadienoate **31** and di-*tert*-butylazodicarboxylate **32** in hot CCl_4 as shown in Scheme 3. After hydrogenation of the double bond and saponification, racemic acid **33** was obtained in 93% yield over 2 steps. The Boc groups were then cleaved with TFA and subsequent *Z* group protection of the *N*(1) atom afforded racemic *N*(1)-*Z*-piperazic acid that was resolved with (+) and (-) ephedrine. (3*R*)-*Z*-piperazic acid **34** was obtained in 18% yield and (3*S*)-*Z*-piperazic acid **39** in 15% yield. To complete the synthesis of dipeptide **21**, (3*R*)-*Z*-piperazic acid **34** was protected with an Fmoc group and converted to acid chloride **36** with oxalyl chloride. A Carpino biphasic coupling with protected hydroxamic acid ester **37** yielded compound **38**. Fmoc-deprotection furnished the desired dipeptide **21** in 62% yield over 3 steps.



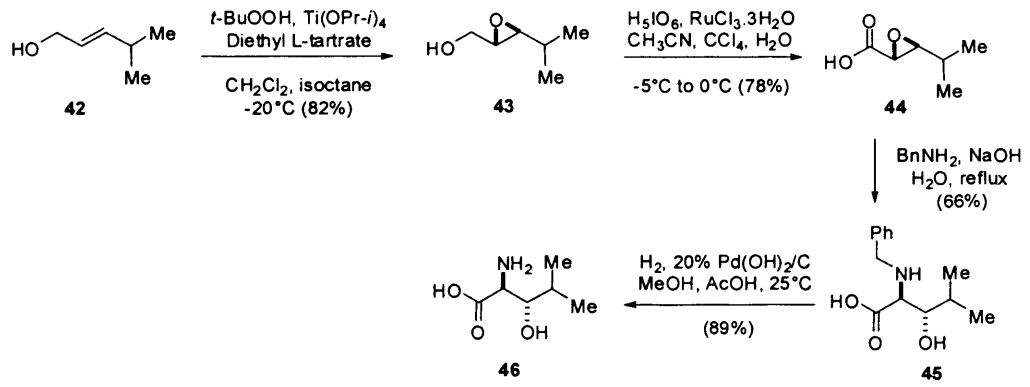
Scheme 3. Synthesis of dipeptide **21**

(3*S*)-*Z*-piperazic acid **39** was protected as a *tert*-butyl ester and the latter condensed with acid chloride **40** using the Carpino two phase aq. $NaHCO_3$/acid chloride coupling conditions (Scheme 4). Finally acid **22** was obtained in 98 % yield after deprotection with TFA.



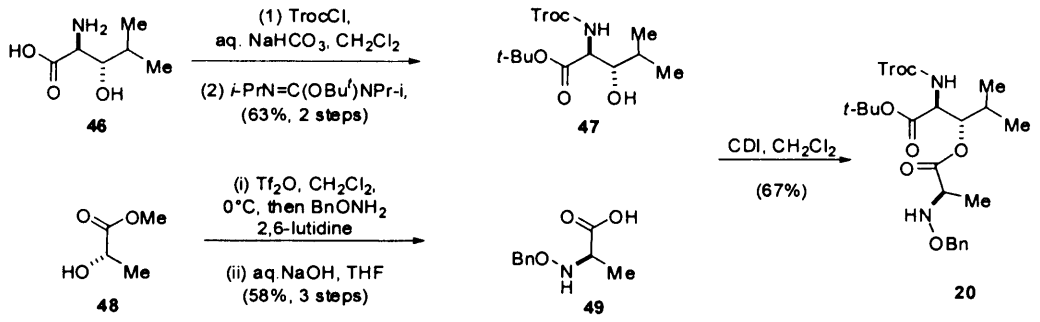
Scheme 4. Synthesis of fragment **22**

To achieve the synthesis of fragment **20**, Caldwell and Bondy developed a synthesis of (2*S*, 3*S*)-3-hydroxyleucine **46** (Scheme 5).[22] It began with a Sharpless asymmetric epoxidation on allylic alcohol **42** to give epoxide **43**. After oxidation of the hydroxyl group, the resulting acid **44** was treated with benzylamine and sodium hydroxide. Regioselective opening of the epoxide occurred in 66% yield to give compound **45**. Finally hydrogenolysis of the *N*-benzyl group afforded (2S, 3S)-3-hydroxyleucine **46** in 89% yield.



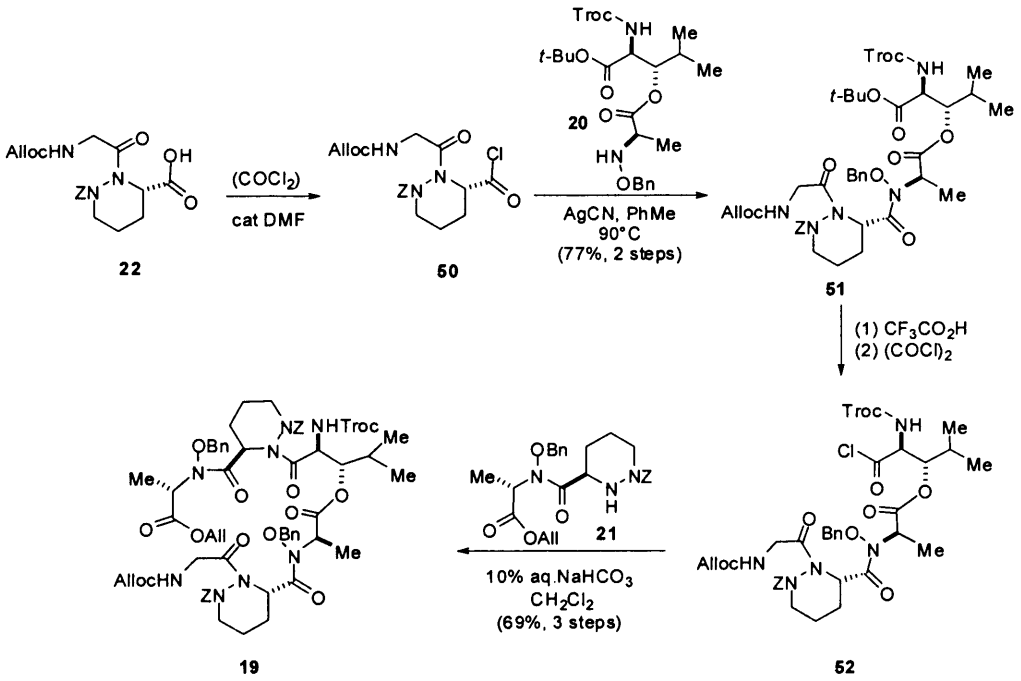
Scheme 5. Caldwell and Bondy's route to (2*S*, 3*S*)-3-hydroxyleucine **46**

The synthesis of fragment **20** was achieved as shown in Scheme 6. (2*S*, 3*S*)-3-hydroxyleucine **46** was protected in 2 steps to afford compound **47** in 68% yield. The latter was condensed with the *N*-hydroxybenzyl-(*R*)-Ala residue **49** in presence of CDI to afford dipeptide **20** in 67% yield.



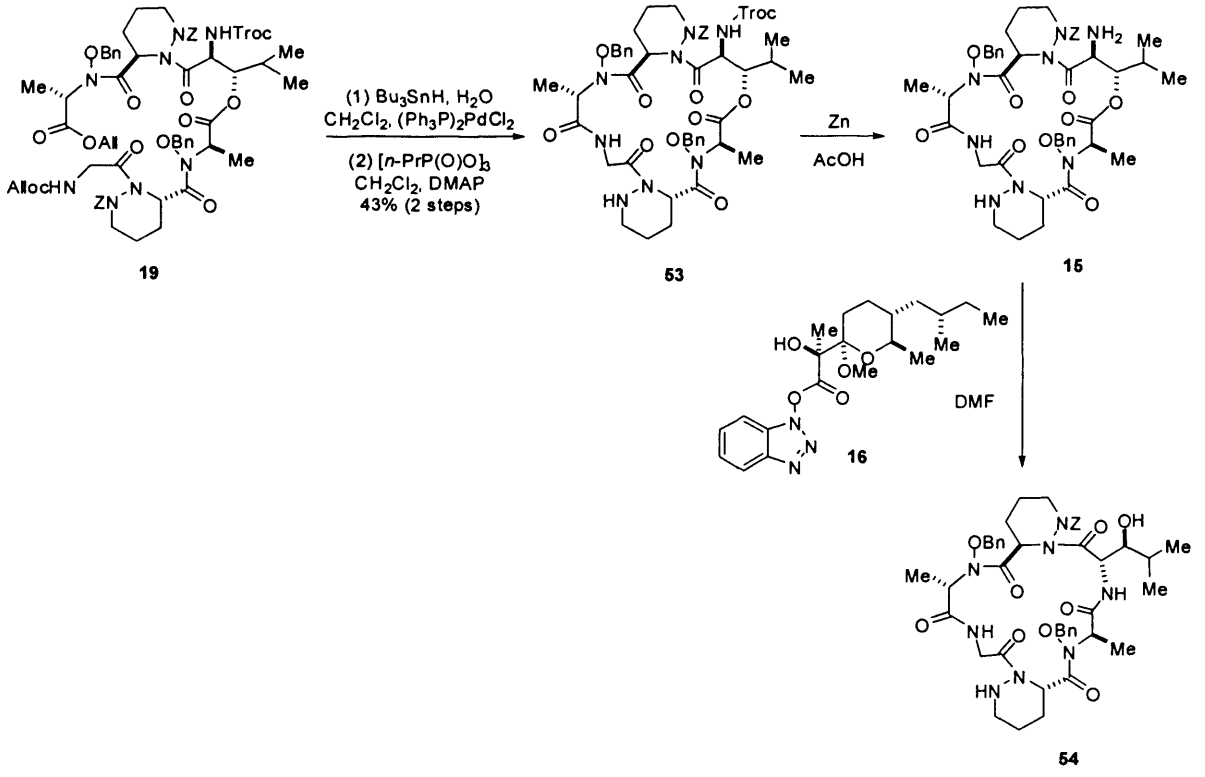
Scheme 6. Synthesis of fragment **20**

After conversion of acid **22** to chloride **50**, the peptide linkage between dipeptide acid chloride **50** and depsipeptide **20** was formed by AgCN-assisted amidation (Scheme 7). The resulting tetrapeptide **51** was then deprotected with TFA and converted into acid chloride **52** using oxalyl chloride. Finally, linear hexapeptide **19** was obtained after coupling with dipeptide **21** using 10% aq. $NaHCO_3$ in 69% over 3 steps.



Scheme 7. Synthetic route to linear hexapeptide **19**

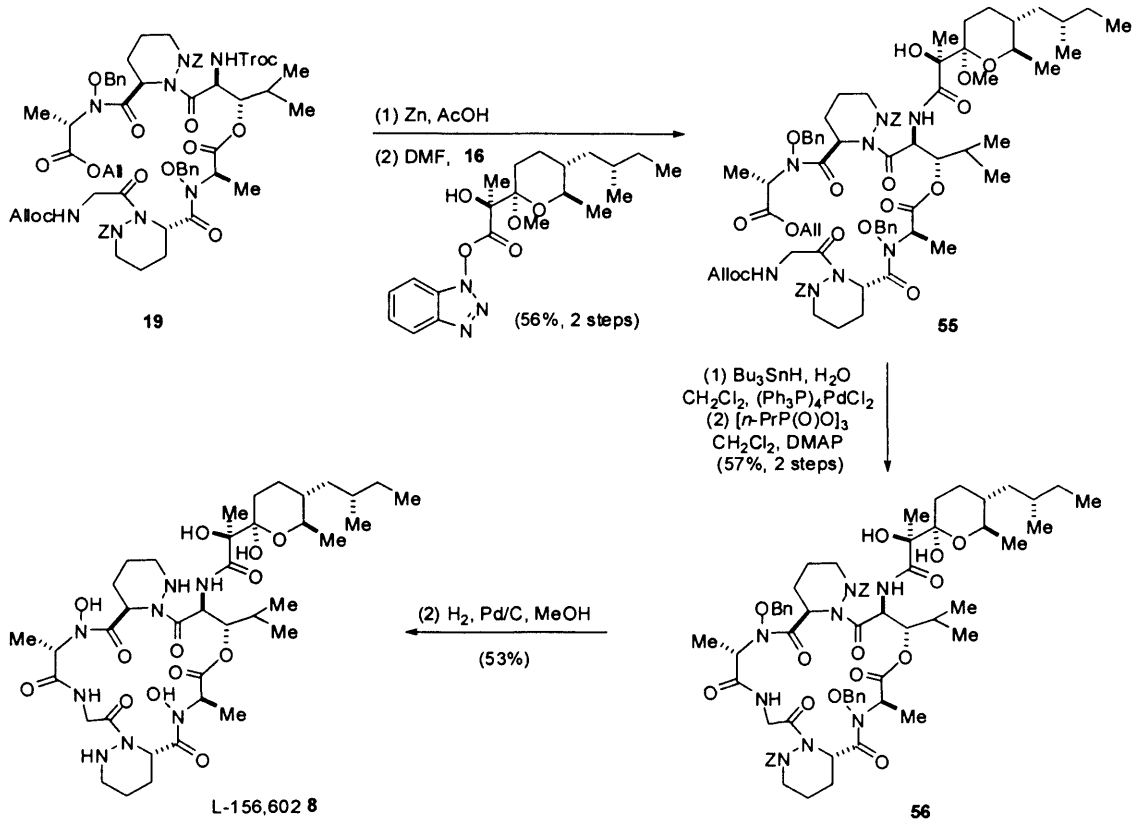
Removal of both the Alloc protecting group and the allyl ester from hexapeptide **19** was achieved in a single step by palladium-catalysed hydrostannolysis (Scheme 8). Cyclisation of the crude resulting hexapeptide was then performed by the mixed phosphonic anhydride method to give cyclodepsipeptide **53**. The Troc group was then cleaved and the resulting free amine **15** coupled with the HOBt activated ester **16**. Unfortunately, the amidation did not succeed, and Cadwell and co-workers isolated the cyclic peptide alcohol **54** resulting from *O,N*-acyl shift.



Scheme 8. Formation of cyclodepsipeptide **15** and attempted coupling with activated ester **16**

The authors revised their retrosynthetic plan and decided to attach the side chain at the linear hexapeptide stage (Scheme 9). The Troc protecting group was cleaved from hexapeptide **19** and the resuting crude amine was reacted with HOBt ester **16** to afford the desired hexapeptide **55** in 56% yield. Deprotection of the Alloc and allyl protective groups by palladium catalysed hydrostannolysis was accompanied by conversion of the methyl pyranoside to the hemiketal. Ring closure was achieved by means of the mixed phosphonic anhydride method to

afford cyclic hexapeptide **56** in 56% yield from linear hexapeptide **55**. Finally, hydrogenolysis of the Z and Bn protective groups gave L-156,602 **8** in 53% yield.

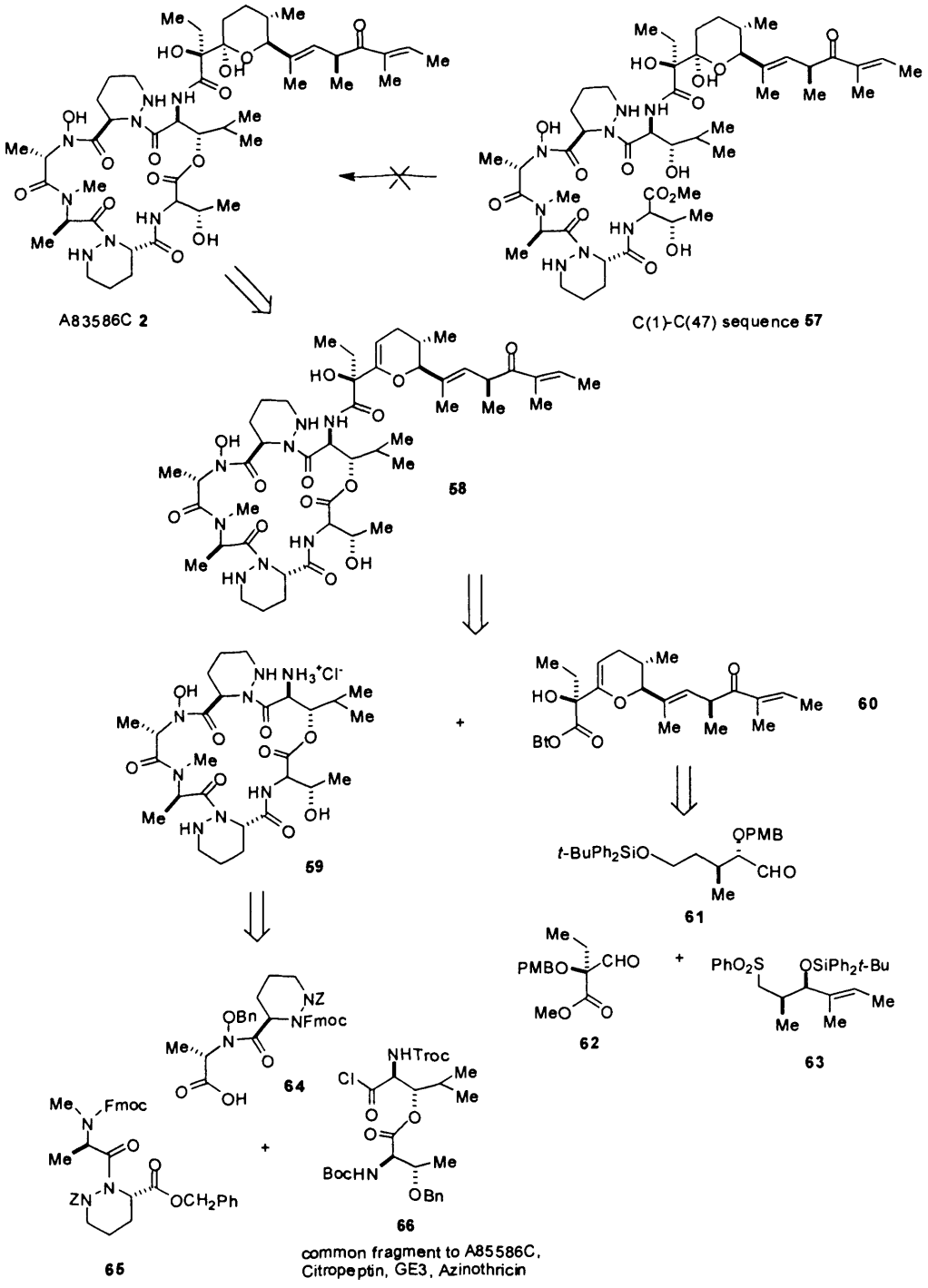


Scheme 9. Completion of the synthesis of L-156,602 **8**

2.1.2. Total Synthesis of A83586C

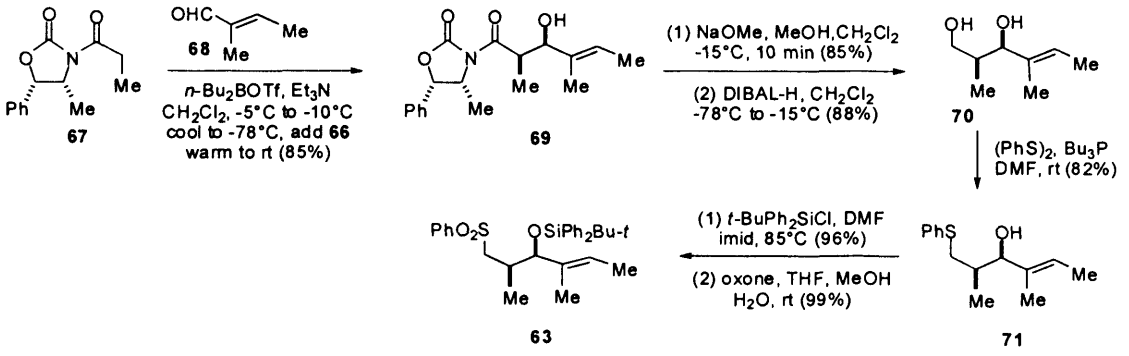
A first retrosynthetic plan of A83586C **2** was elaborated; the C(1)-C(47) **57** sequence was synthesised (Scheme 10).[23] Unfortunately difficulties occurred in the macrolactamisation and new ways of synthesis were considered. In 1997, our group achieved the first total synthesis of A83586C through an endgame that exploited a highly chemoselective coupling between the fully elaborated cyclodepsipeptide **59** and the activated pyran ester **60**.[24] The last two steps were the union of an activated ester **60** with a pre-assembled, unprotected cyclodepsipeptide **59** followed by a chemoselective hydration of the resulting glycal **58** under

very mild acidic conditions with wet deuterochloroform. A [2+2+2] condensation strategy was used to prepare cyclodepsipeptide **59** from peptides **64**, **65** and **66**. The synthesis required a total of 95 individual steps, but because it was highly convergent, the longest linear sequence was only of 28 steps.



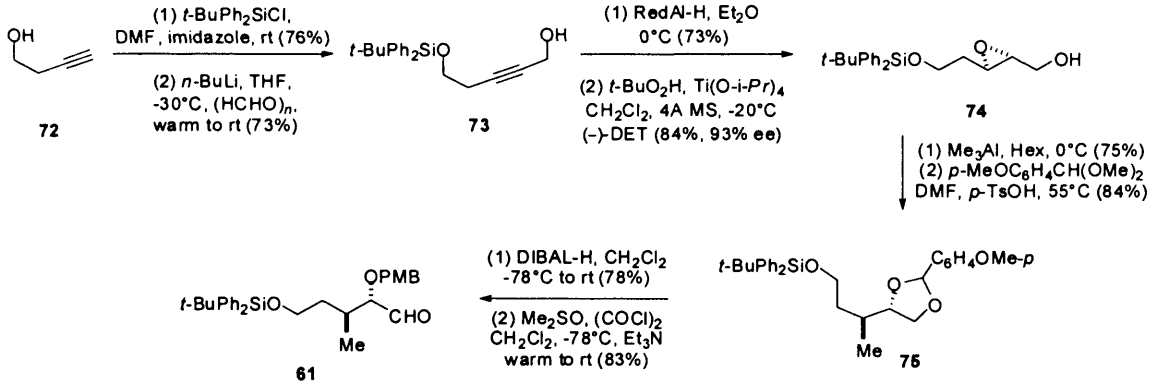
Scheme 10. Retrosynthetic analysis of A83586C

Synthetic planning for the pyran sector was centred on the preparation of intermediates **61**, **62** and **63**. Sulfone **63** was obtained from compound **67** as shown in Scheme 11. An Evans asymmetric aldol reaction between oxazolidinone **67** and aldehyde **68** afforded compound **69**.[25] The chiral auxiliary was cleaved from compound **69** with sodium methoxide. The resulting methyl ester was reduced with DIBAL-H to afford diol **70**. Selective thioesterification of the primary alcohol with tributylphosphine and phenyldisulfide provided **71** and after *O*-silylation and Trost-Curran oxidation with oxone, compound **63** was obtained in a 50% overall yield.



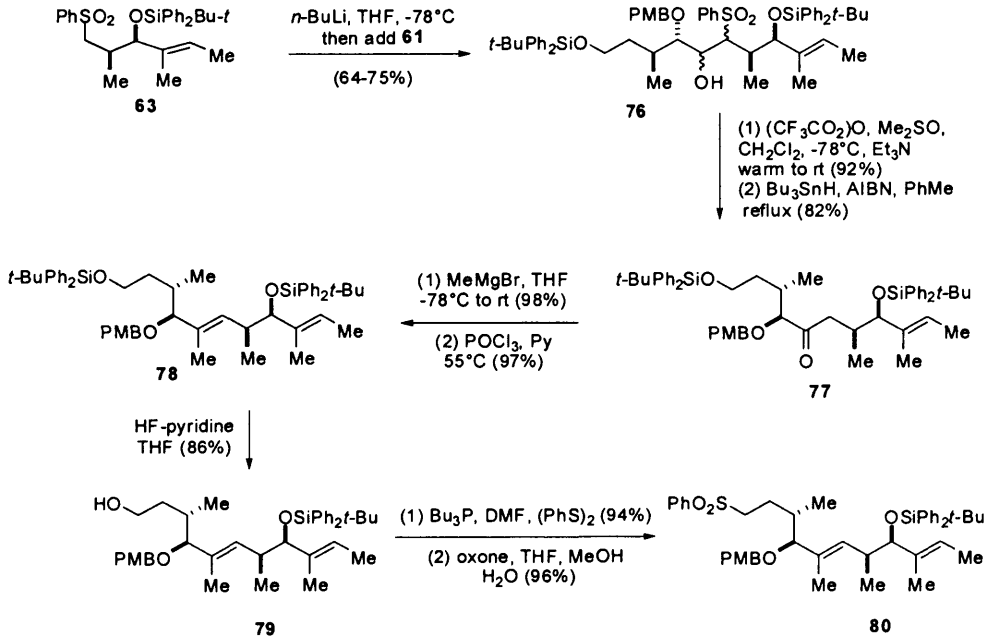
Scheme 11. Synthesis of sulfone **63**

Two key reactions were used to install the *anti*-relationship of the two adjacent stereocentres in compound **61** (Scheme 12). First, a Sharpless asymmetric epoxidation was used to prepare the chiral 2,3-epoxy alcohol **74**. Then, a chelation-controlled epoxide ring-opening reaction with trimethylaluminium was performed. It proceeded with 20:1 selectivity in favour of the C(3)-ring opened product. Protection of the diol as *p*-methoxybenzylidene, cleavage of the obtained acetal and Swern oxidation of the resulting primary alcohol gave aldehyde **61**.



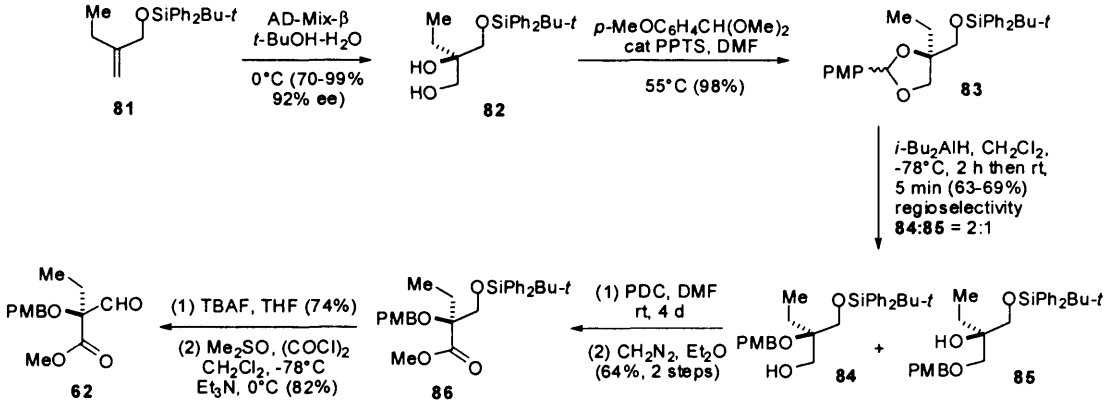
Scheme 12. Synthesis of aldehyde **61**

Unification of sulfone **63** and aldehyde **61** was successfully performed with *n*-BuLi (Scheme 13). The resulting β-hydroxysulfone **76** was oxidised with trifluoroacetic anhydride and DMSO. The resulting β-ketosulfone was reduced with AIBN / tri-*n*-butylstannane to give ketone **77**. Alkene **78** was formed from compound **77** *via* a Grignard addition followed by $POCl_3$-pyridine mediated dehydration. Compound **78** was obtained as the major isomer in a 2.6:1 mixture with the 1,1-disubstituted alkene. Cleavage of the primary silyl group and sulfonation of the obtained alcohol provided compound **80**.



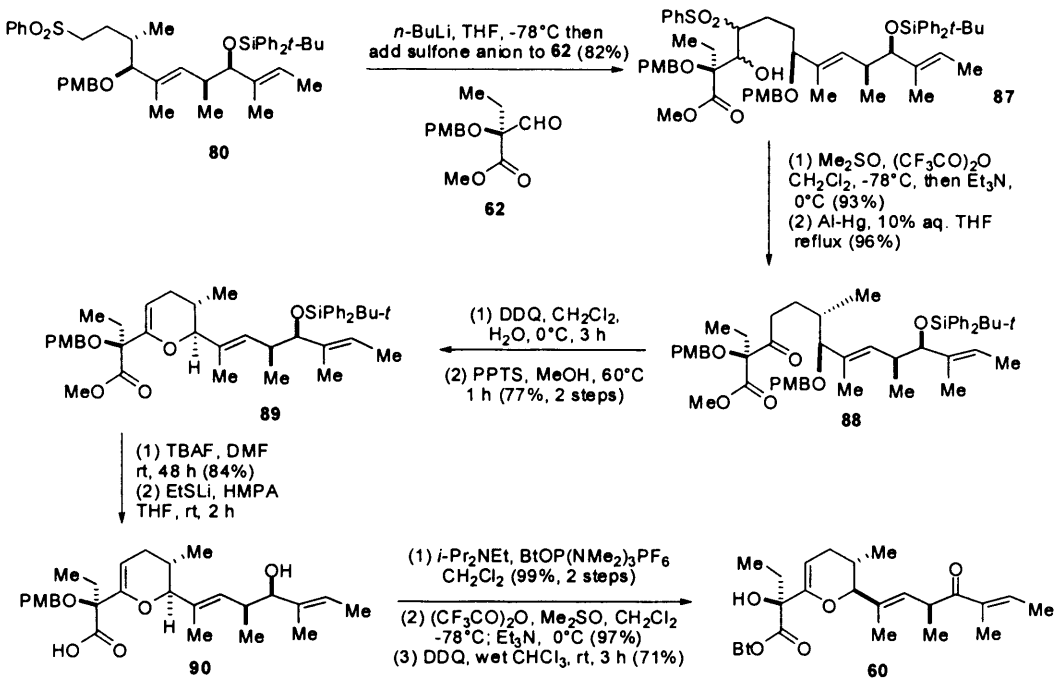
Scheme 13. Synthesis of compound **80**

The synthesis of fragment **62** is shown in Scheme 14. The stereochemistry of the chiral diol **82** was obtained from alkene **81** by a Sharpless catalytic asymmetric dihydroxylation reaction. A strategy involving formation of a *p*-methoxybenzylidene followed by acetal reduction was used to position a PMB group preferentially on the more hindered hydroxyl. Alcohols **84** and **85** were readily separated by flash chromatography. Alcohol **84** was oxidised and esterified to deliver the methyl ester **86**. The last steps involved deprotection of the silyl group and oxidation of the resulting alcohol under Swern conditions.



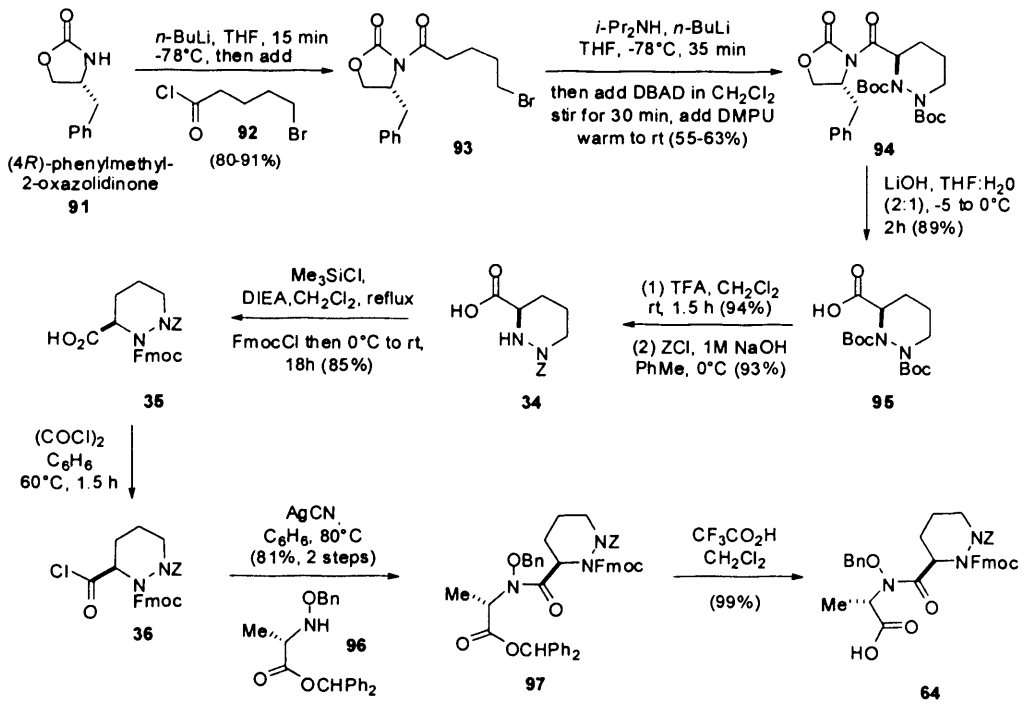
Scheme 14. Synthesis of β-aldehydo ester **62**

The last steps of the preparation of activated ester **60** are illustrated in Scheme 15. The β-hydroxysulfone **87** formed by condensation of sulfone **80** and aldehyde **62** was subjected to Swern oxidation. Reduction of the resulting β-ketosulfone proceeded efficiently with aluminium amalgam in aqueous THF to give compound **88**. A regioselective *O*-debenzylation was next attempted with DDQ in aqueous CH_2Cl_2 at 0° C. It furnished a mixture of the β-hydroxyketone and the two α- and β-ring-closed hemiketals, which was treated with PPTS and methanol to give the glycal **89**. Deprotection of the alcohol followed by conversion of the methyl ester to the acid afforded compound **90**. Construction of the activated ester **60** was thereafter accomplished by treatment with Castro's BOP reagent, Swern oxidation, and deprotection of the tertiary PMB ether with DDQ in wet chloroform.



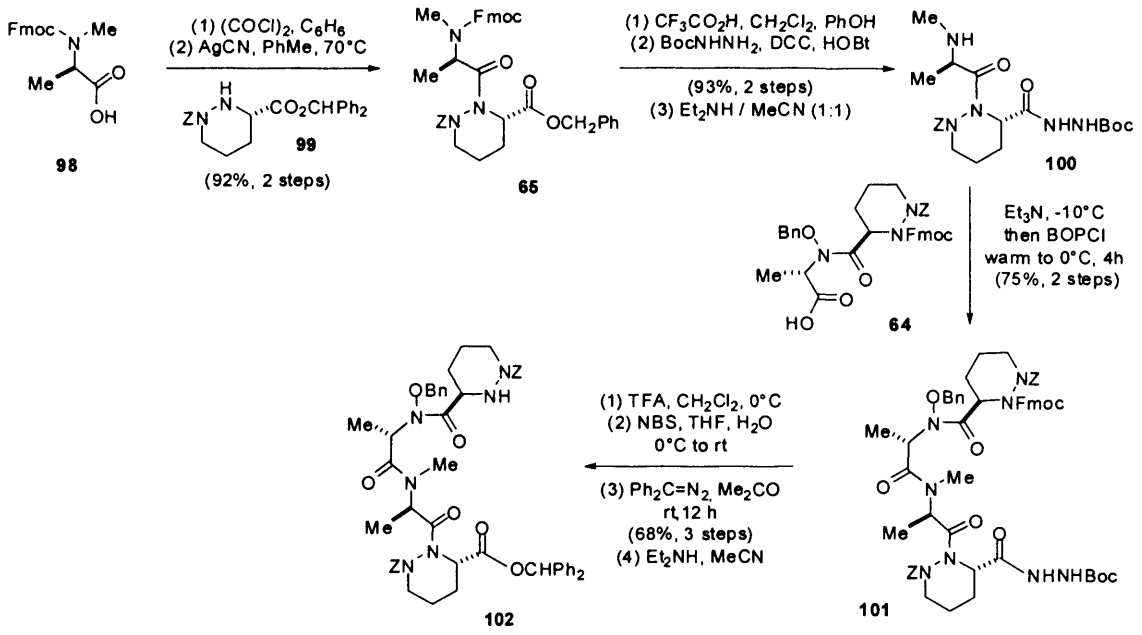
Scheme 15. Synthesis of the pyran sector of A83586C

During the A83586C project, the Hale group had to find new methods for the synthesis of many of the key units of A83586C. Indeed the first short enantioselective synthesis of both (3*R*)- and (3*S*)-piperazic acids was developed.[26] The (3*R*)-piperazic acid and (3*S*)-piperazic acid were synthesised *via tandem* electrophilic hydrazination-asymmetric nucleophilic cyclisation.[26] The synthesis of *N*(1)-*Z*-(3*R*)-piperazic acid **34** is illustrated in Scheme 16. The route commenced with a regioselective deprotonation of (4*R*)-phenylmethyl-2-oxazolidinone **91** and subsequent *N*-acylation with bromovaleryl chloride **92**. The resulting bromide **93** was treated with LDA to produce an internally-coordinated enolate that underwent a stereoselective hydrazination with di-*tert*-butylazodicarboxylate (DBAD). Tandem cyclisation occured after addition of DMPU to afford compound **94**. *N*(1)-*Z*-(3*R*)-piperazic acid **34** was obtained after removal of the auxiliary using lithium hydroxide, cleavage of both Boc groups with TFA and *Z* group protection of the *N*(1)-atom. Dipeptide **64** was obtained *via* a silver cyanide coupling between the acid chloride **36** derived from *N*(1)-*Z*-*N*(2)-Fmoc-(3*R*)-piperazic acid **35** with the glycine derivative **96**. Deprotection of the acid with TFA yielded dipeptide **64**.



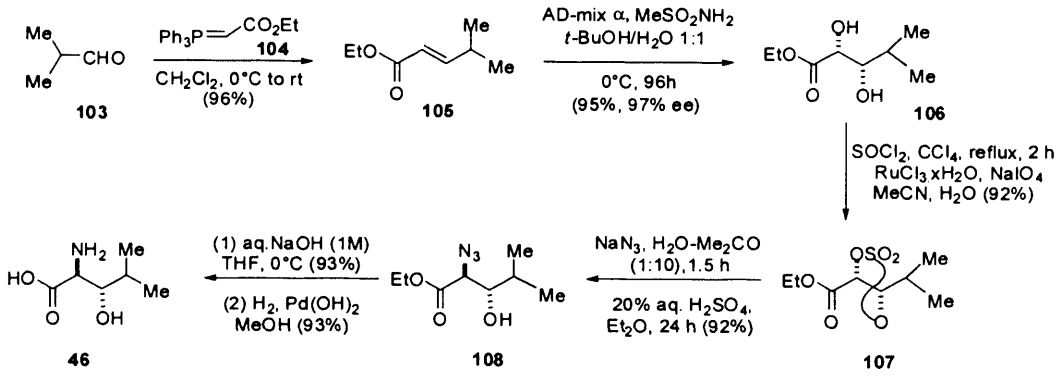
Scheme 16. Syntheses of *N*(1)-*Z*-(3*R*)-piperazic acid **34** and dipeptide **64**

The same silver cyanide assisted amidation methodology was used to couple the (3*S*)-piperazic acid derivative **99** to the acid chloride of Fmoc-*N*(Me)-D-Ala **98** to yield compound **65** (Scheme 17). For both these procedures, the amino-acid chloride was used in its Fmoc-protected form because first, these Fmoc amino-acid chorides are very stable and easy to prepare but also because they are highly reactive and able to couple to donors with low nucleophilicity with minimum epimerisation at the α-stereocentre. However, difficulties were later encountered upon removal the Fmoc protecting group from **65** leading to the formation of the diketopiperazine. Replacement of the diphenyl methyl ester group from compound **65** with a *t*-butylcarbazide function avoided that problem. Peptidic coupling of the resulting amine **100** with acid **64** activated with BOP-Cl/Et_3N afforded compound **101**. The Boc group was removed with TFA and the resulting acyl hydrazine oxidised to the acid with NBS.[27] Esterification with diphenyldiazomethane followed by cleavage of the Fmoc group with diethylamine gave compound **102**.



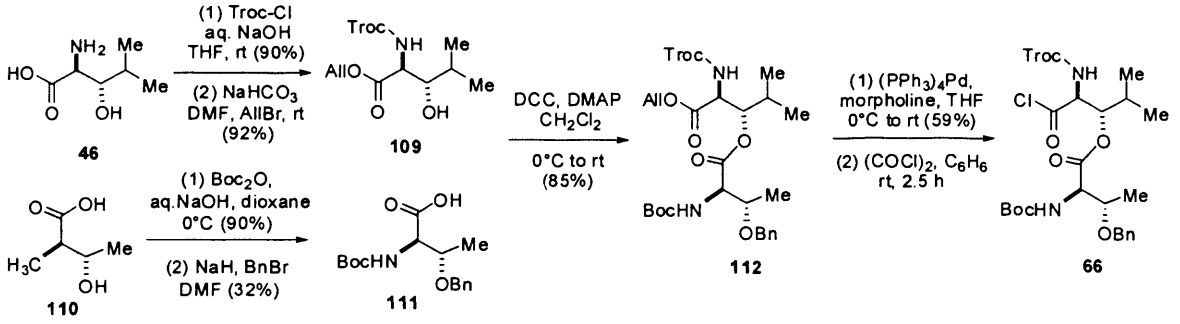
Scheme 17. Formation of compound **102**

Dipeptide **66** contains the (2*S*,3*S*)-3-hydroxyleucine moiety and is common to the five antibiotics described at the beginning of this section. A novel large scale synthesis of (2*S*,3*S*)-3-hydroxyleucine **46** was developed by the Hale group for the synthesis of A83586C.[28] This new method, depicted in Scheme 18, requires only 6 steps and begins with a Wittig condensation between isobutyraldehyde **103** and carboethoxymethylene triphenylphosphorane **104** to afford alkene **105**. An efficient entry into the chiral *anti*-amino alcohol motif was achieved by use of the Sharpless asymmetric dihydroxylation reaction.[29] The resulting diol **106** was converted with thionyl chloride to its 2,3-cyclic sulfite that was oxidised *in situ* into sulfate **107** with $RuCl_3/NaIO_4$. A ring opening strategy using NaN_3 afforded azido ester **108** in 92% yield. Hydrolysis of the ester with aqueous sodium hydroxide followed by hydrogenation afforded (2*S*,3*S*)-3-hydroxyleucine **46**.



Scheme 18. Synthesis of (2*S*,3*S*)-3-hydroxyleucine **46**

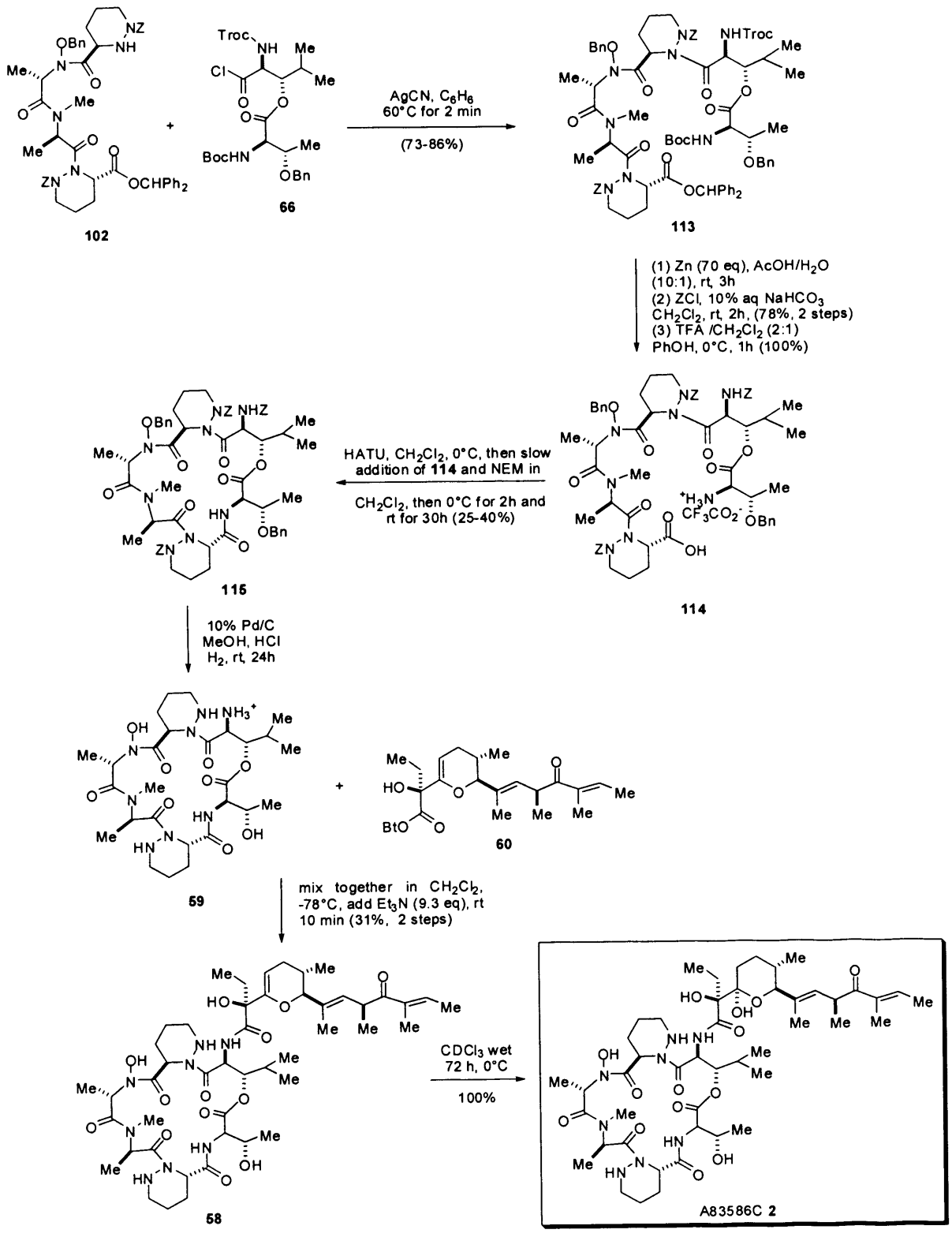
Compound **112** was then obtained via a DMAP-assisted DCC coupling of the protected derivative **109** with acid **111**. *O*-Deallylation of **112** with Pd(0) and morpholine followed by treatment with oxalyl chloride provided the depsipeptide acid chloride **66** (Scheme 19).



Scheme 19. Synthesis of depsipeptide **66**

The final steps of the synthesis of A83586C are shown in Scheme 20. The coupling of chloride **66** to amine **102** was achieved efficiently (86% yield) with silver cyanide at 60 °C to afford peptide **113**. The reaction needed to be conducted for 2 min otherwise decomposition quickly ensued. The Troc group was then detached with Zn dust and replaced with a Z group. A mild acidolysis with TFA and phenol was used to cleave the Boc and the diphenylmethyl groups and generate compound **114**. The phenol trapped out the diphenylmethyl cation and prevented it from causing unwanted side reactions. After screening many activation reagents unsuccessfully, macrolactamisation of compound **114** was eventually accomplished with HATU and *N*-ethylmorpholine in CH_2Cl_2 under conditions of very high dilution[30] in 25-40% yield. The

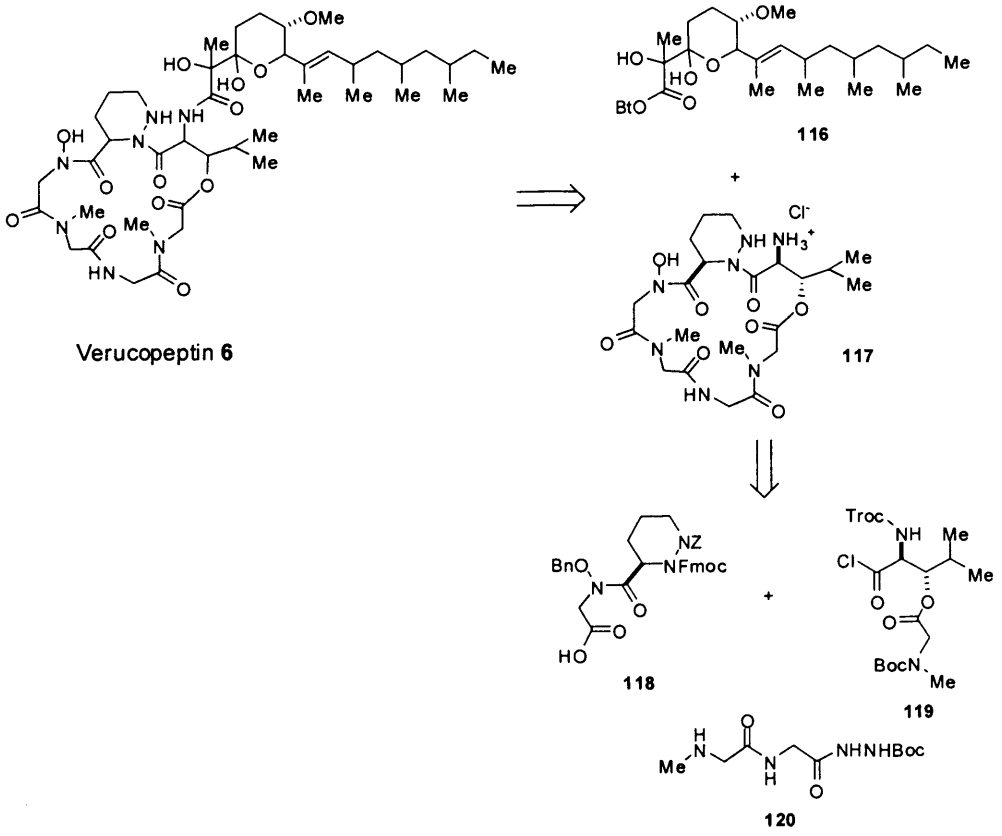
benzyl protecting groups were then cleanly deprotected by catalytic hydrogenation over a 10% Pd on carbon catalyst in methanol containing 1% eq of HCl. This acidic medium helped prevent *O*- to *N*-acyl shift from occuring in the *β*-hydroxyleucine residue. The last steps of the synthesis consisted in the union of the crude cyclodepsipeptide core **59** with the activated ester **60**. Both were suspended in CH_2Cl_2 and after cooling that mixture to -78 °C, Et_3N was added and the reaction mixture warmed to room temperature and stirred for 10 minutes. Compound **58** was obtained in 31% yield after chromatography purification. Finally compound **58** was hydrated with wet deuterochloroform to deliver A83586C **2** in a quantitative yield.



Scheme 20. Total synthesis of A83586C **2**

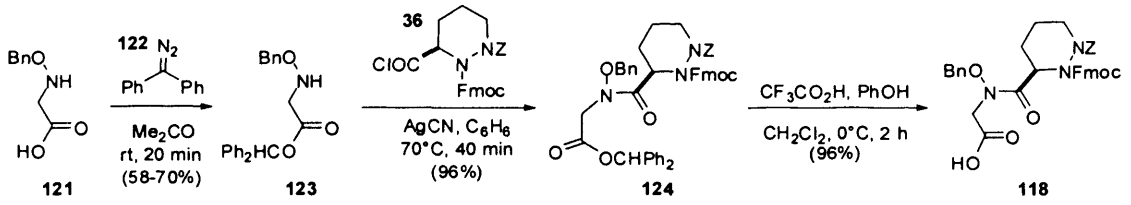
2.1.3. Synthesis of Verucopeptin Cyclodepsipeptide Core

In 2001, our group reported a synthesis of the cyclodepsipeptide core of verucopeptin **6**.[31] This antitumour antibiotic incorporates a more functionalised pyran sector than other members of the azinothricin family but a greatly simplified cyclodepsipeptide core. Achieving its synthesis could pave the way for the synthesis of simplified analogues. The relative and absolute configurations of verucopeptin remain currently unknown. Hence it was decided to synthesise the diastereoisomer that was closest in structure to the other members of the family i.e. the isomer containing a (3*R*)-piperazic acid unit linked to a (2*S*,3*S*)-3-hydroxyleucine. With the experience gained during the A83586C synthesis, a [2+2+2] fragment condensation strategy was planned to link the linear hexapeptide domain. This strategy would also involved a union between fragments **116** and **117**. Fragment **117** could be obtained by successive coupling between compounds **118** and **120**, removal of the Fmoc group from the resulting tetrapeptide and union with fragment **119** using acid chloride coupling technology (Scheme 21).



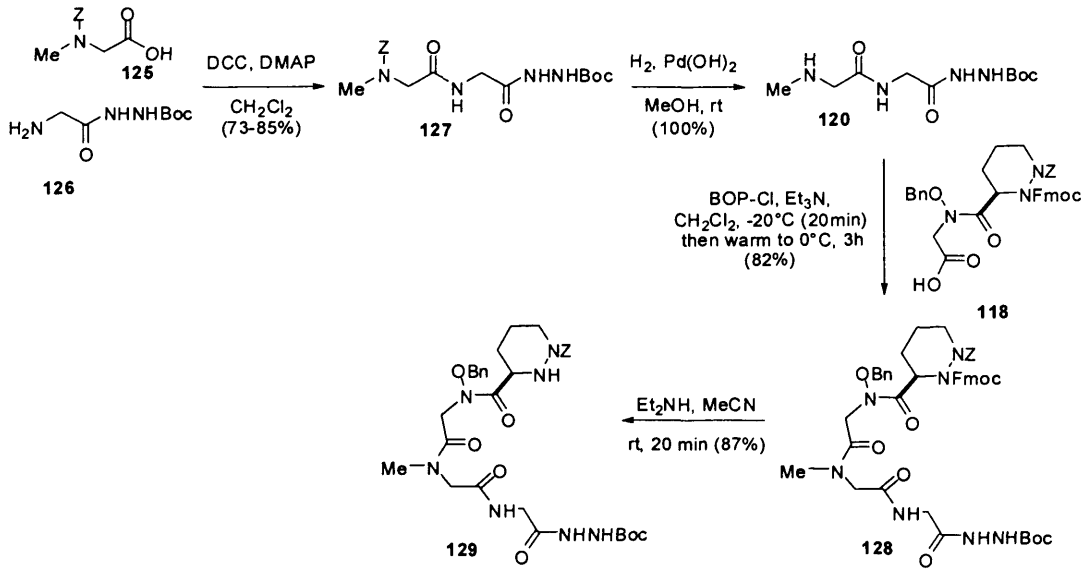
Scheme 21. Retrosynthetic plan of verucopeptin **6**

The synthesis of peptide **118** commenced from the protected hydroxamic acid **121**, the synthesis of which was reported by Kolasa and Chimiak.[32] Compound **121** was esterified with diphenyldiazomethane **122** to afford compound **123**. Silver cyanide assisted coupling with acid chloride **36**, followed by removal of the diphenylmethyl ester group of **124** gave acid **118** (Scheme 22).



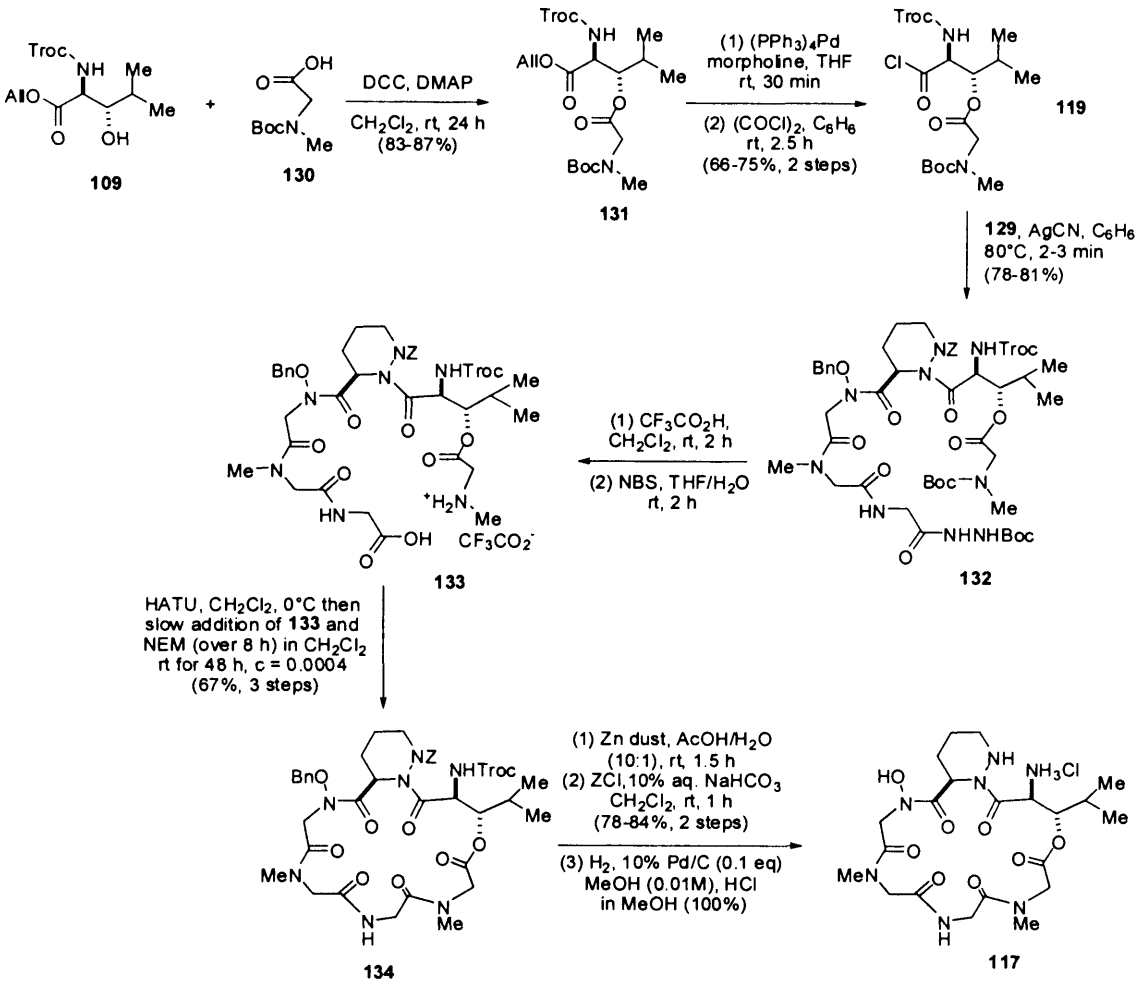
Scheme 22. Synthesis of peptide **116**

The peptide linkage of tetrapeptide **127** was built by a DMAP-assisted DCC coupling between compounds **125** and **126** (Scheme 23). Removal of the Z group followed by coupling of the resulting amine **120** with compound **118** using BOP-Cl and Et_3N afforded compound **128**. Subsequent cleavage of the Fmoc group gave tetrapeptide **129** in 87% yield.



Scheme 23. Synthesis of tetrapeptide **129**

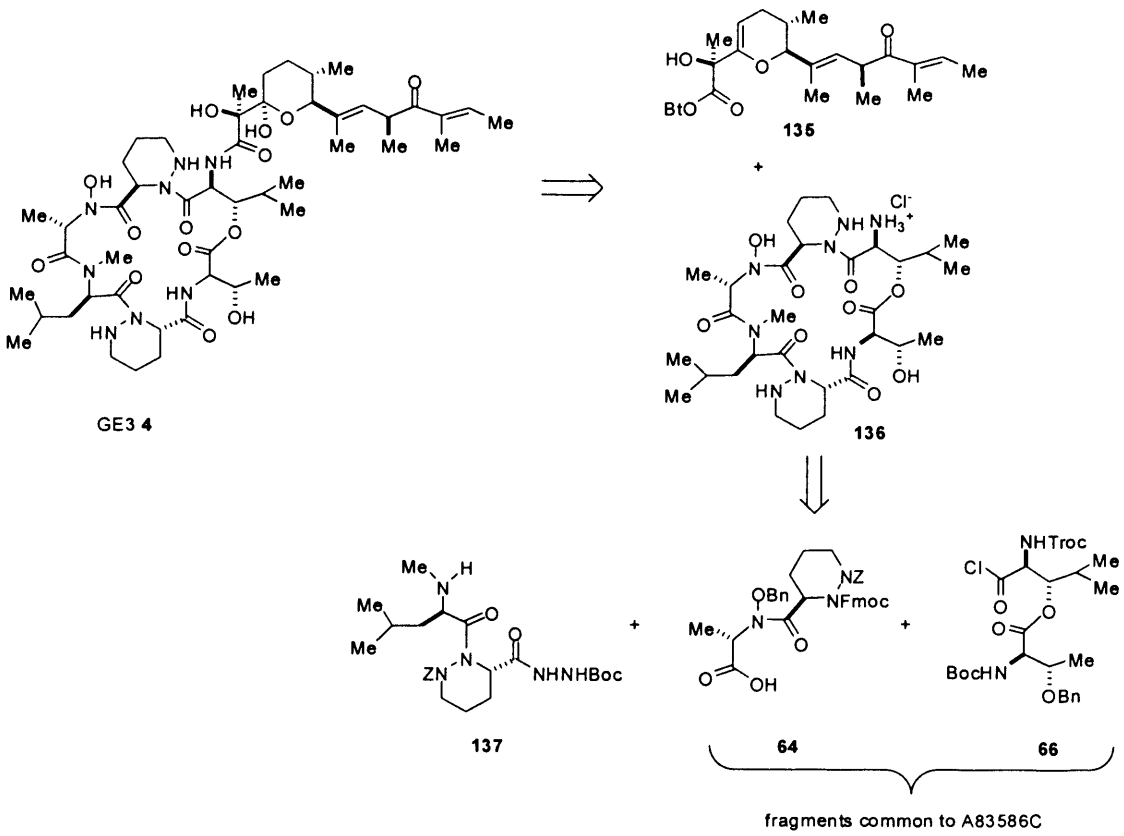
To complete the preparation of cyclodepsipeptide **117**, the synthesis of acid chloride **119** still had to be accomplished (Scheme 24). A DCC-DMAP mediated *O*-esterification between alcohol **109** and acid **130** provided ester **131**, which was submitted to deallylation with Pd(0)/morpholine and chlorination with oxalyl chloride to give acid chloride **119**. The coupling between compounds **119** and **129** took place efficiently (80% yield) when silver cyanide was used as the promoter and the mixture was heated at 80 °C for 2-3 min. Hexapeptide **132** was then converted to the amino acid **133** by TFA treatment followed by chemoselective oxidation of the Gly acyl hydrazide group with NBS.[27] Contrary to the A83586C synthesis, the macrolactamisation had to be carried out before *N*-Troc to *N*-Z group interconversion otherwise degradation occurred under the basic Z-protection conditions. The cyclisation was performed using Carpino's HATU protocol[30] and cyclodepsipetide **134** was obtained in 67% yield over 3 steps. The Troc-urethane was then detached with Zn dust and successfully replaced with a Z group using benzylchloroformate and 10% aqueous $NaHCO_3$. Catalytic hydrogenation in methanol in the presence of one equivalent of HCl afforded cyclodepsipeptide **117**.



Scheme 24. Synthesis of Verucopeptin cyclodepsipeptide core **117**

2.1.4. Synthesis of GE3 Cyclodepsipeptide Core

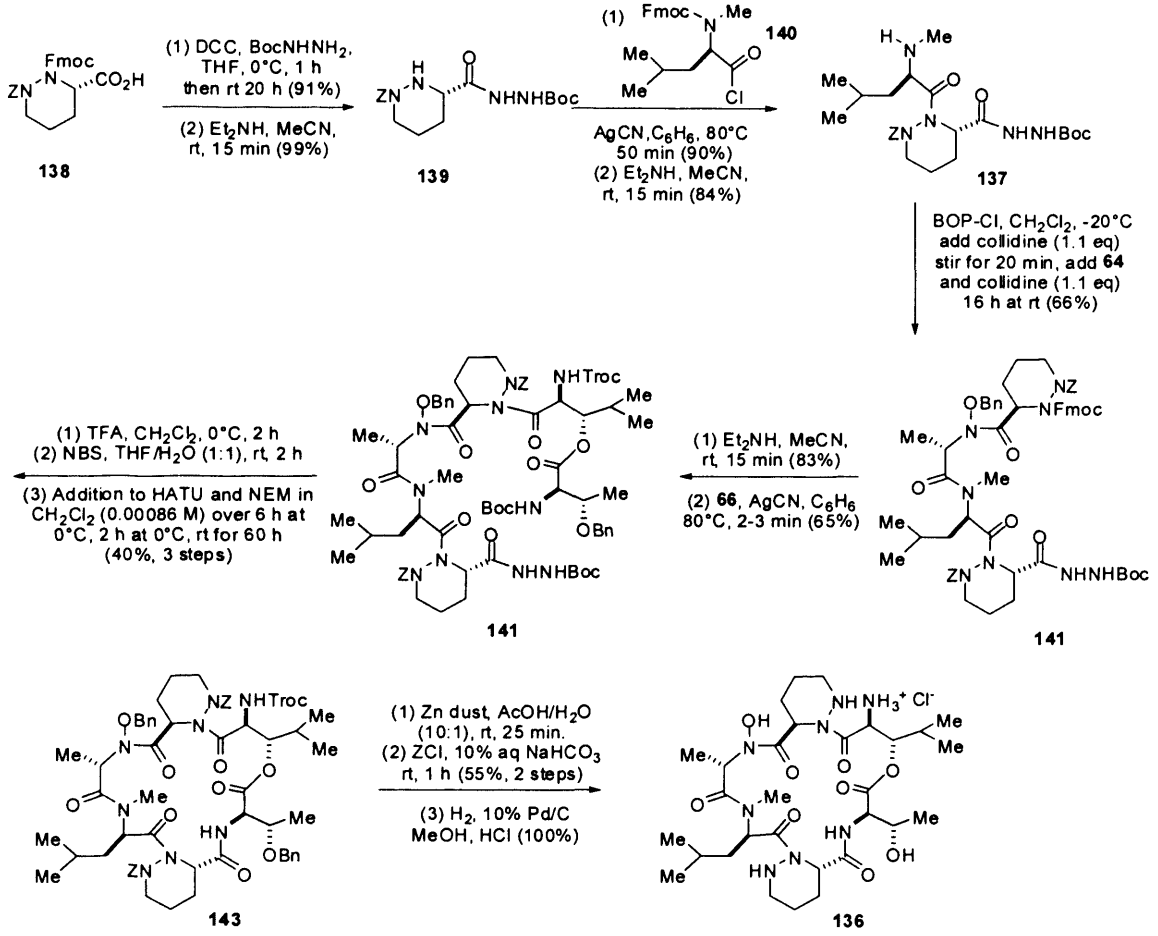
In 2002, our group achieved the synthesis of the GE3 cyclodepsipeptide. The retrosynthetic plan which was based on the synthesis of A83586C, is shown in scheme 25. It also involved a [2+2+2] fragment condensation strategy and utilised two of the three dipeptide components that were used for the synthesis of A83586C.



Scheme 25. Retrosynthetic analysis of the GE3 cyclodepsipeptide

The synthesis of tetrapeptide **137** is depicted in Scheme 26. It started from the (3*S*)-*N*(1)-Z-*N*(2)-Fmoc-piperazic acid **138** which was protected with a *t*-butylcarbazide function using DCC as the condensing agent. The Fmoc group was then detached to allow **139** to be coupled with acid chloride **140** in presence of silver cyanide. Tetrapeptide **137** was obtained after cleavage of the Fmoc group. All efforts to couple tetrapeptide **137** to acid **64** using the BOP-Cl/NEt_3 system which was so efficient in the A83586C synthesis, failed. After having tried a wide range of conditions, it was discovered that the combination of BOP-Cl and collidine could yield the desired tetrapeptide **141** in 66% yield. The Fmoc group was then cleaved from **141**, and the third fragment, **66**, was attached using silver cyanide to give peptide **142**. After the cleavage of the two Boc group, the *N*-acyl hydrazine was oxidised with NBS/water to give the acid. The macrolactamisation was achieved using the same conditions as for A83586C, i.e. with HATU in very high dilution in CH_2Cl_2, as developed by Carpino. It proceeded in a 40% yield over three steps from compound **142.** The last steps involved replacing the Troc group with a Z group and

deprotecting the three Z-groups by hydrogenolysis under mildly acidic conditions to give the cyclodepsipeptide **136**.



Scheme 26. Preparation of the GE3 cyclodepsipeptide **136**

2.2. Previous Syntheses of Analogues of the Azinothricin Family of Antibiotics

The synthesis of analogues of A83586C is of interest as these may be of value for elucidating the mode of antitumour action of these natural products. In fact, by testing analogues, it should be possible to determine which part of the molecule is essential for potent antitumour activity. Analogue work might also allow a considerably simplified structure to be identified that has good antitumour properties and which can be more readily synthesised industrially. Some cyclodepsipeptides analogues have already been synthesised: the 4-*epi*-analogue[33] **144** is one such compound, as is the L-proline modified A83586C **145**.

The 4-*epi*-analogue **144** has a (3*R*)-piperazic acid component replacing the (3*S*)-piperazic acid unit (Figure 5). Making this change improved the yield of the macrolactamisation from 25% to 70% but the 4-*epi*-analogue **144** was much less active as an antitumour drug. It is believed that in that analogue, the C(8)-carbonyl adopts a conformation *cis* to the C(7), whereas the relationship between these two bonds is *trans* in A83586C.

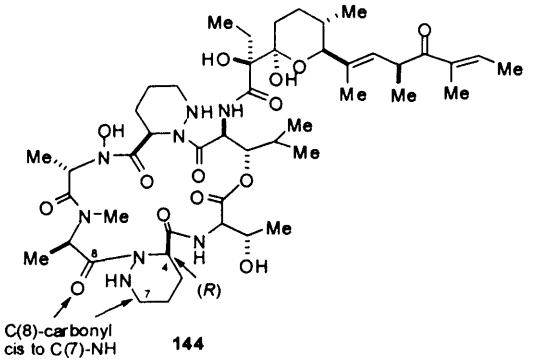
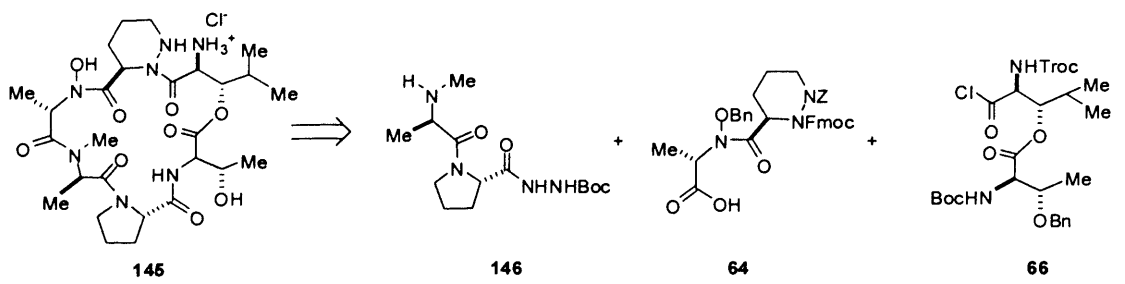


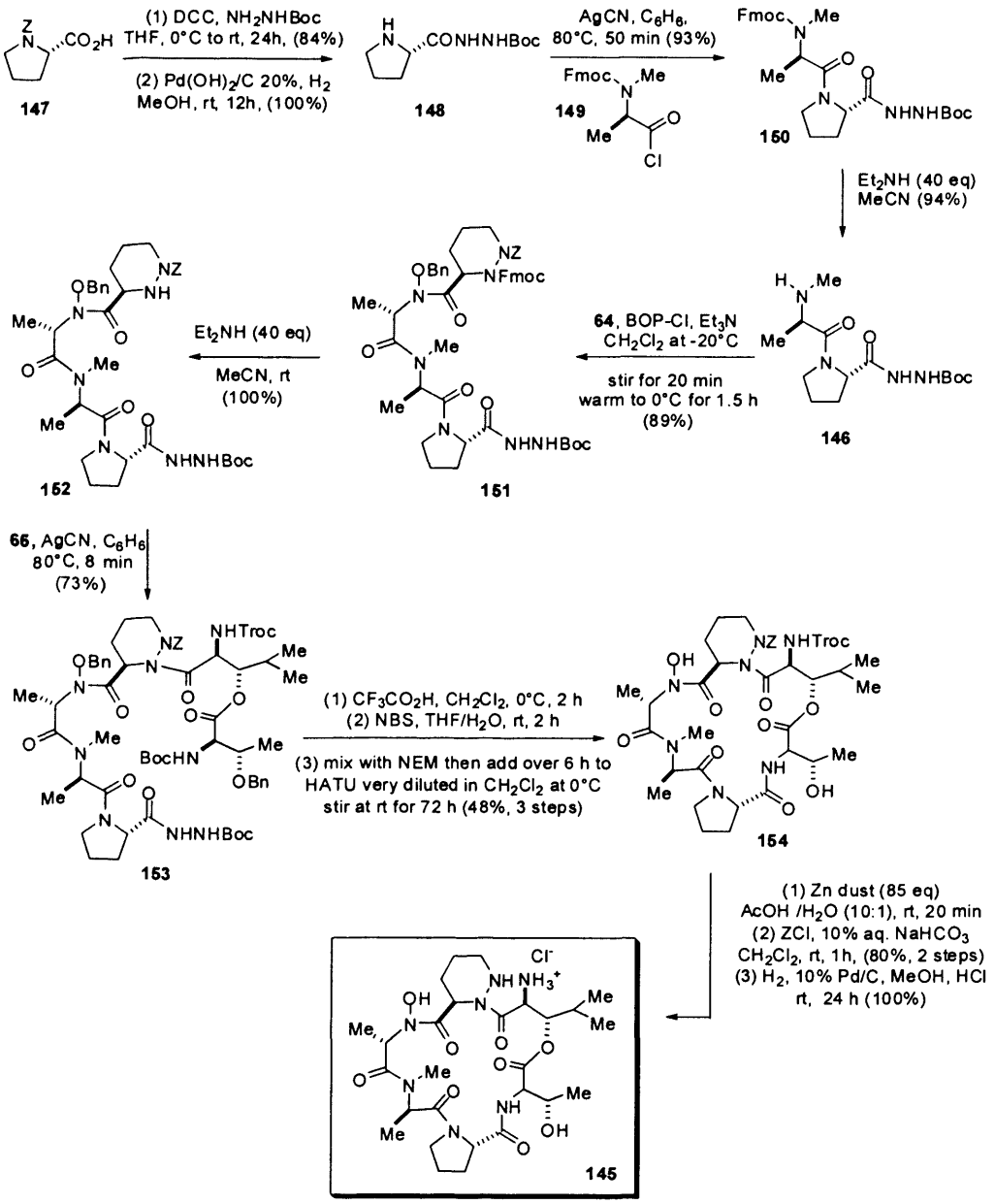
Figure 5. 4-*epi*-A83586C **144**

For this reason, it was decided to synthesise an analogue that had similar conformational properties than A83586C. The L-proline analogue was selected, because, first, the (3*S*)-piperazic acid has previously functioned as a very effective mimic of L-proline in ACE-inhibitor such as cilazaprill[34] and secondly, cyclisation at an activated proline residue is usually free of racemisation risk. The synthesis of the L-proline modified mimetic of the A83586C cyclodepsipeptide **145** was thus performed in our laboratory in 2002.[35] The strategy involved coupling of fragments **146**, **64**, and **66** as shown in Scheme 27.



Scheme 27. Retrosynthetic plan to the L-proline modified mimetic of the A83586C cyclodepsipeptide **145**

Units **64** and **66** of A83586C were used for the synthesis of cyclodepsipeptide **145**. Dipeptide **146** was prepared from *N*-Z-L-proline **147** as shown in Scheme 28. The latter was converted to the acyl hydrazide **148** by treatment with $BocNHNH_2$/DCC followed by catalytic hydrogenation to cleave the Z group. A peptide bond was formed by silver cyanide assisted coupling between Fmoc-*N*-methyl-D-alanyl-chloride **149** and compound **148** to afford compound **150**. Fmoc cleavage afforded amine **146** which was purified and readily coupled to acid **64** by treatment with BOPCl and Et_3N at low temperature. Fmoc deprotection followed by condensation of tetrapeptide **152** with acid chloride **66**, using silver cyanide as a promoter, gave hexapeptide **153** in 73% yield. The last stages of the synthesis were performed in the same order as for verucopeptin and GE3 cyclodepsipeptides: the two Boc groups were cleaved with TFA, the liberated *N*-acylhydrazine was converted to the acid with NBS, and the macrolactamisation was carried out at very high dilution utilising HATU as the carboxyl activating reagent. Macrolactam **154** was obtained in 48% yield over 3 steps. Acquisition of cyclodepsipeptide **147** was accomplished after Z replacement of the Troc group and hydrogenation over Pd/C in the presence of one equivalent of HCl in MeOH.

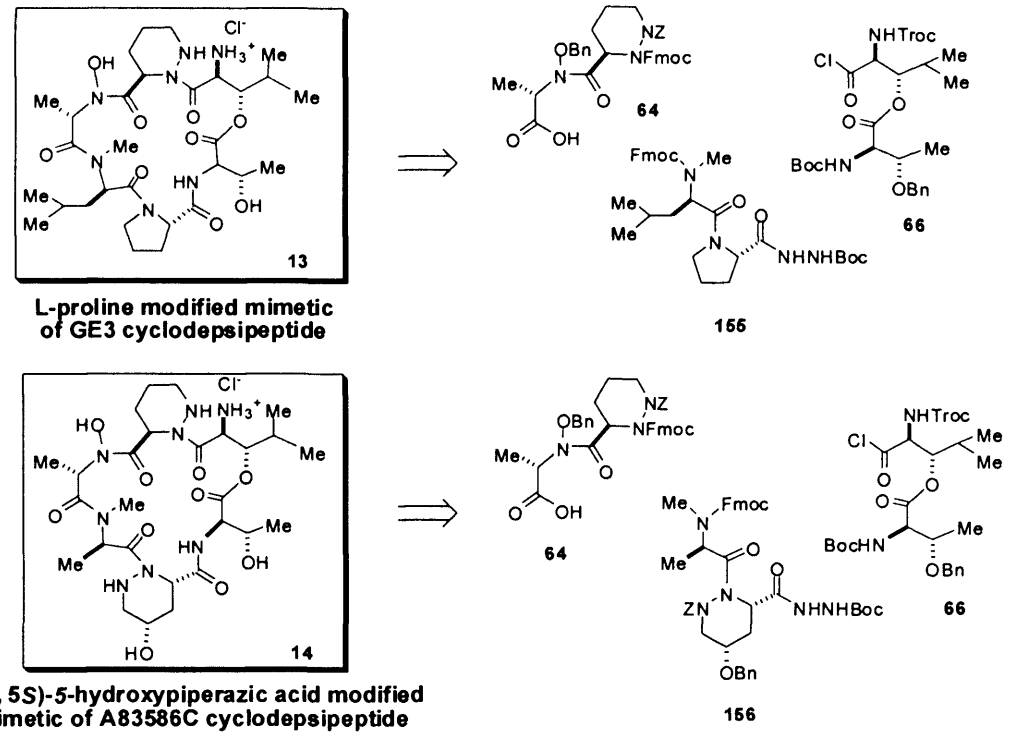


Scheme 28. Synthesis of the L-proline modified mimetic of the A83586C cyclodepsipeptide **145**

3. Synthetic Studies Towards Analogues of the Azinothricin Family

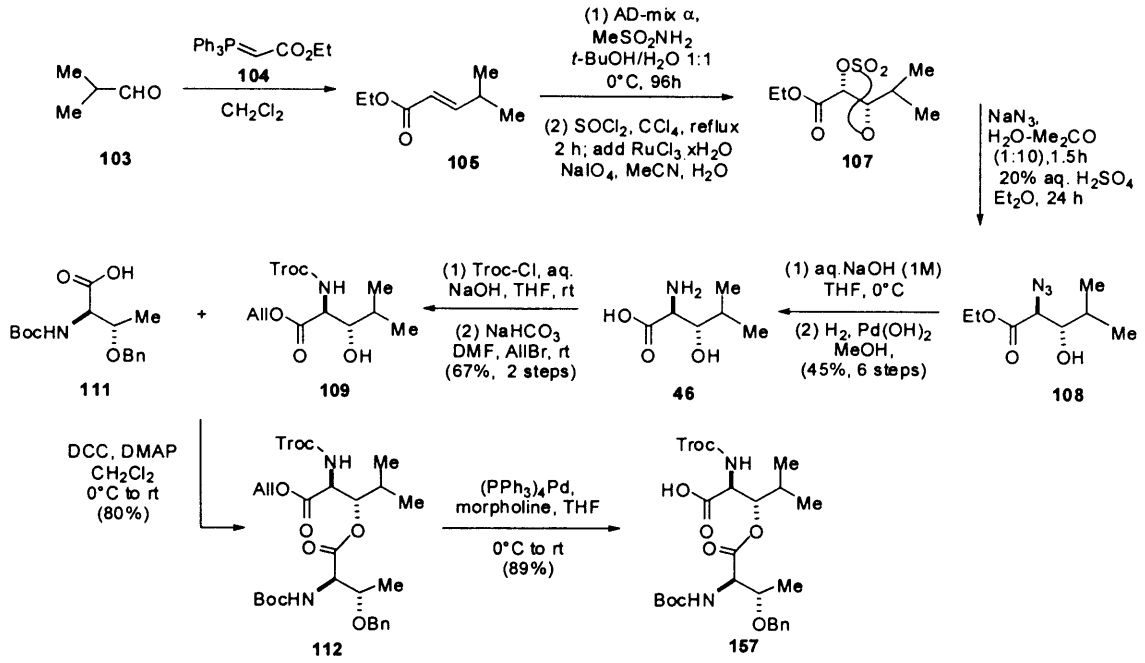
As outlined in the introduction, our group had developed a large knowledge concerning the synthesis of molecules of the Azinothricin family at the outset of this project and so was now in a very good position to exploit this knowledge for constructing more analogues. As a member of this research program, I worked on the synthesis of two modified cyclodepsipeptides. The L-proline modified mimetic of GE3 cyclodepsipeptide **13** was chosen because: (a) GE3 was the most potent E2F inhibitor to have been discovered so far and we considered that its proline congener is likely to have promising properties. (b) comparing its biological activity with the already synthesised L-proline modified mimetic of A83586C would help to uncover which features of these molecules were essential for activity and; (c) the structure being simpler, the synthesis could potentially be more readily achieved on a large scale as was required for possible industrial applications.

We also selected the (3*S*, 5*S*)-5-hydroxypiperazic acid modified mimetic of A83586C, **14**, in order to analyse how the biological and pharmacokinetic properties of a more hydrophilic molecule would vary; a key problem with molecules of the A83586C class is their poor water solubility. Adding an extra hydroxyl might improve this situation and give a more readily administered drug. The retrosynthetic analyses of these two cyclodepsipeptides are depicted in Scheme 29.



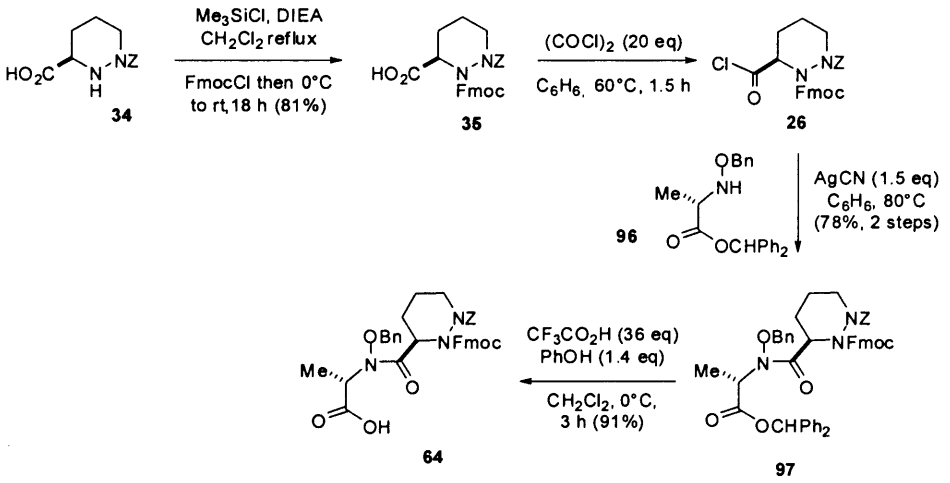
Scheme 29. Retrosynthetic plan to two cyclodepsipeptides

Again, a [2+2+2]-fragment condensation strategy would be adopted. Two of the three fragments are common to both cyclodepsipeptides and their syntheses had already be developed for the A83586C synthesis. Thus, a large part of this project is dedicated to large scale synthesis. To access dipeptide **66**, the 6 step synthesis of hydroxyleucine **46** was performed on a multigram scale without purification by chromatography (Scheme 30). Hydroxyleucine **46** was obtained in 45% yield from isobutyraldehyde **107**. The detail of each step was described earlier in the introduction. Then, the DMAP-assisted DCC coupling yielded dipeptide **60**, which was deprotected using Pd(0) and morpholine to afford acid **157** in 89% yield. Acid **157** would be converted into chloride **66** just before use. The spectral data obtained for acid **157** corresponded to that published by our group during the GE3 cyclodepsipeptide synthesis.[36] 40 g of the protected hydroxyleucine **109** was synthesised.



Scheme 30. Synthesis of acid **157**

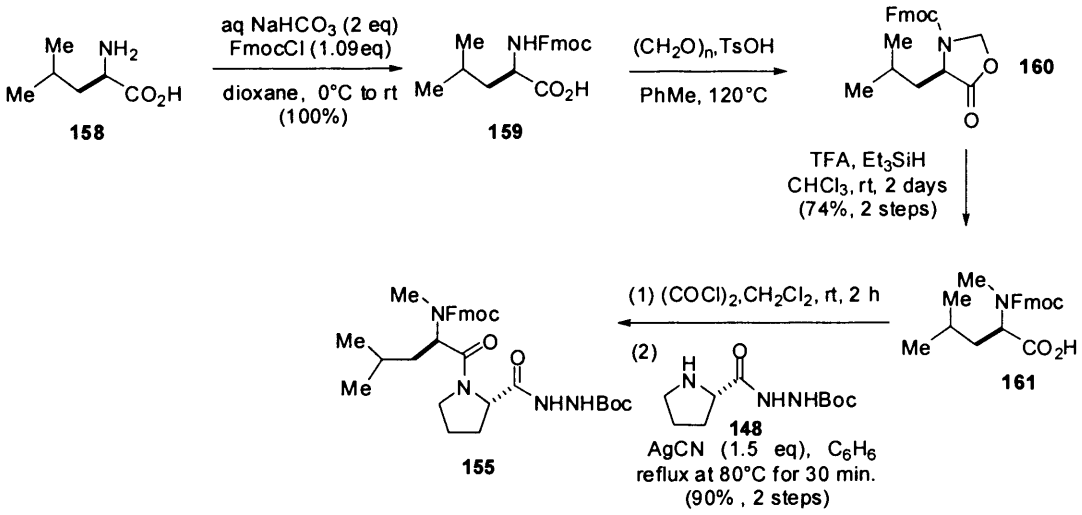
Compound **64** was prepared using the route developed in the A83586C synthesis (Scheme 31). Compounds **34** and **96** were already prepared by L. Lazarides of this group.[36] Protection of **34** was achieved in a good yield using FmocCl in presence of diisopropylethylamine and trimethylsilyl chloride. The acid was converted to its chloride and combined with **96** in a silver cyanide mediated coupling. The acid group of compound **97** was then deprotected with TFA to afford acid **64**.



Scheme 31. Synthetic route to compound **64**

3.1.Synthesis of an L-proline analogue of GE3 cyclodepsipeptide

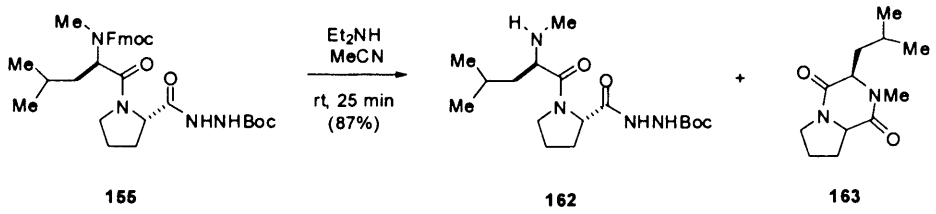
The synthetic route to dipeptide **155** is depicted in Scheme 32. It started from commercially available D-leucine **158**.[37] An Fmoc group was attached to amine **158** with Fmoc-Cl and sodium carbonate in dioxane. Addition of water and ether to the reaction mixture, acidification of aqueous layers and extraction with diethyl ether allowed isolation of acid **159**. The latter was cyclised using paraformaldehyde in presence of phenol in toluene at 120°C using a Dean-Stark apparatus. Treatment of crude oxazolidinone **160** with TFA / Et_3SiH in chloroform liberated the Fmoc protected *N*-methylamine **161** which was obtained in 74% yield over 2 steps after crystallisation. The 500 MHz ^1H NMR spectrum of compound **161** in $CDCl_3$ indicated the presence of two rotamers. The formation of the peptide linkage between amine **148** and the acid chloride of **161** was carried out using silver cyanide at 80 °C in benzene for 30 min to provide dipeptide **155** in 90% yield over 2 steps.



Scheme 32. Synthesis of fragment **155**

Fmoc deprotection of dipeptide **155** was achieved with diethylamine (35 eq) in MeCN at room temperature for 35 minutes. After purification of the crude residue by silica gel chromatography, deprotected dipeptide **162** could not be isolated pure. TLC analysis showed that a faster moving product had formed during the purification. The presence of 10% of

diketopiperazine **163** was detected by ^{1}H NMR analysis of the mixture obtained after flash chromatography (Scheme 33).



155 162 163

Scheme 33. Removal of the Fmoc group from compound **155**

A second purification by SiO_2 flash chromatography of the mixture allowed isolation of pure diketopiperazine **163**. However, dipeptide **162** could never been separated from some diketopiperazine **163**. 500 MHz ^{1}H NMR spectrum of the mixture of **162** and **163** in $CDCl_3$ is shown in Figure 6 and 500 MHz ^{1}H NMR spectrum of diketopiperazine **163** in $CDCl_3$ is shown in Figure 7. In the ^{1}H NMR spectrum of diketopiperazine **163** in $CDCl_3$, the lack of singlet around δ 1.40 ppm indicated the absence of the *tert*-butyl group. Additionally, the signal corresponding to the N-Me group in diketopiperazine **163** is shifted downfield compared to **162** due to the proximity of the carbonyl group.

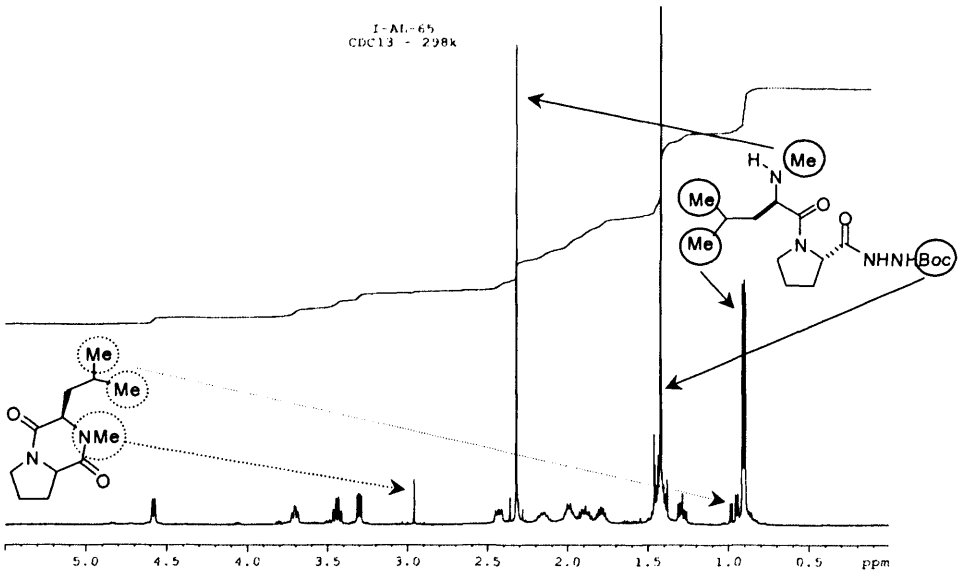


Figure 6. ^{1}H NMR spectrum of the mixture containing dipeptide **162** with 10% of diketopiperazine **163** in $CDCl_3$ at 298K

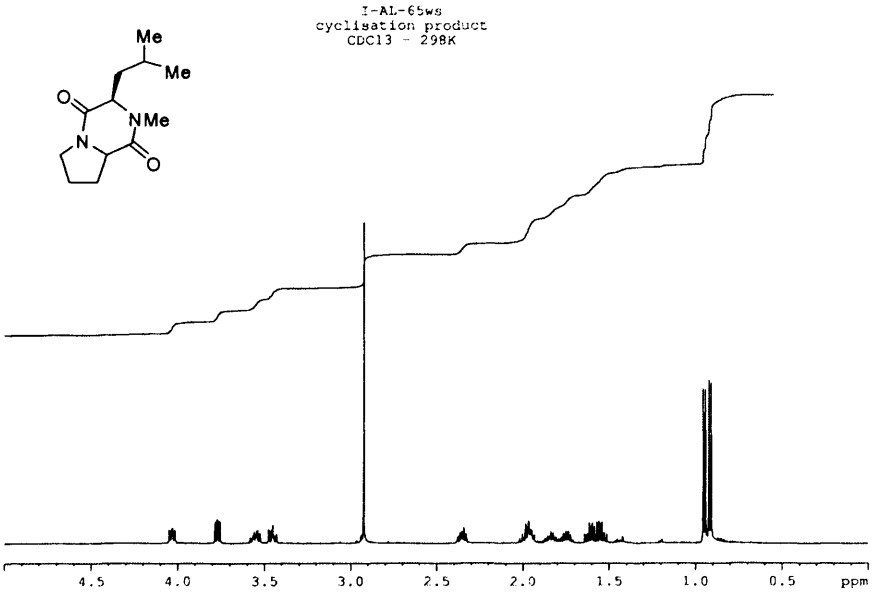
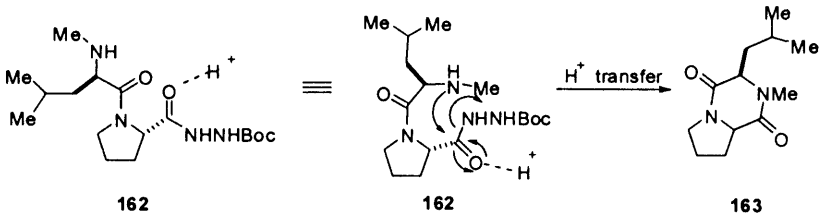


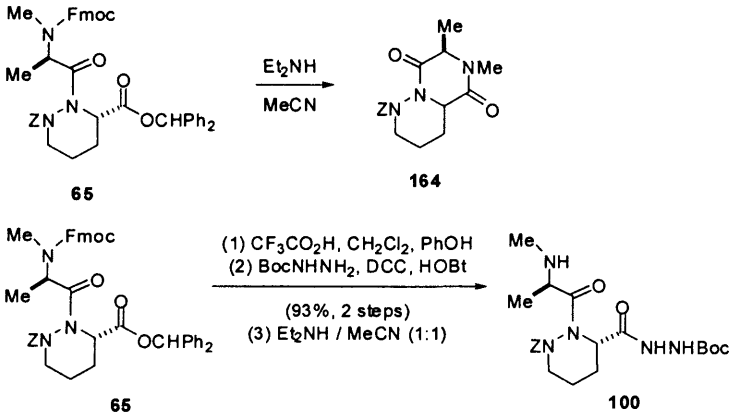
Figure 7. ^{1}H NMR spectrum of **163** in $CDCl_3$ at 298K

It is believed that the formation of diketopiperazine **163** is triggered by the acidity of the silica as shown in Scheme 34.



Scheme 34. Mechanism of formation of diketopiperazine **163**

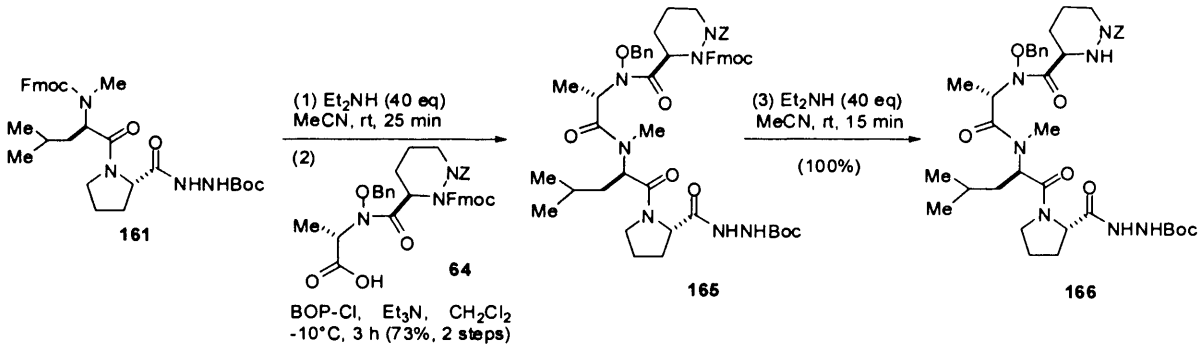
A diketopiperazine formation was observed at the same stage of the synthesis of A83586C[24] (Scheme 35). However, the acid was protected with the more labile Ph_2CH ester group and the diketopiperazine formation was avoided by replacement of the Ph_2CH ester group with a BocNHNH group.



Scheme 35. Formation of diketopiperazine **164** observed in the A83586C synthesis

Attempts to couple the purified dipeptide **162** (with 10% of diketopiperazine **163**) to acid **64** remained unsuccessful. This difficulty was overcome by coupling crude dipeptide **162** and acid **64** with BOPCl and NEt_3 at -10°C in dichloromethane (Scheme 36). Tetrapeptide **165** was obtained in 73% yield over 2 steps; its formation was easily followed on the TLC plate with the appearance of a yellow spot with anisaldehyde. The formation of tetrapeptide **165** was confirmed by FAB HRMS analysis which contained an $(M+Na)^+$ peak at m/e 1024.48548 (Calcd $(M+Na)^+$ for $C_{55}H_{67}N_7NaO_{11}$ 1024.47960). Tetrapeptide **165** was then deprotected using

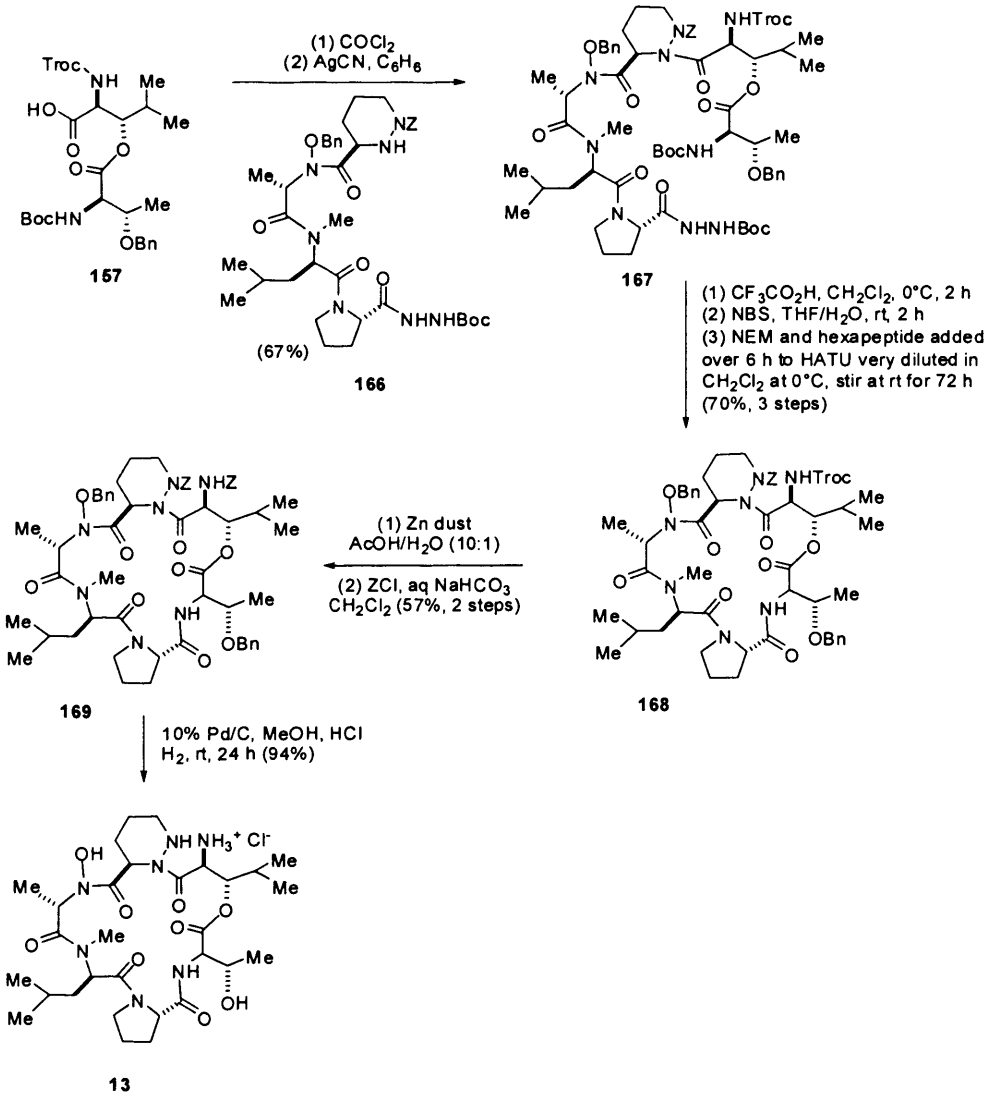
diethylamine (40 eq) in MeCN at room temperature for 25 minutes to afford **166** in quantitative yield.



Scheme 36. Synthesis of tetrapeptide **166**

The final steps of the synthesis of cyclodepsipeptide **13** are shown in Scheme 37. Acid **157** was first converted to chloride **66**. The [4+2] condensation was achieved by heating chloride **66** with tetrapeptide **166** in the presence of AgCN in C_6H_6 at 80°C. It is important to stop heating this reaction after 5 min, otherwise decomposition might ensue. The structure of the resulting compound **167** was confirmed by FAB HRMS analysis which contained an $(M+Na)^+$ peak at m/e 1396.54502 (Calcd $(M+Na)^+$ for $C_{65}H_{90}N_9NaO_{17}$ 1396.54176). In fact, the ^1H NMR and ^{13}C NMR spectra of **167** were complex due to the presence of rotamers. The conversion of hexapeptide **167** to cyclodepsipeptide **168** was performed in 70% yield using the 3-step protocol developed in this research program. The Boc groups were cleaved by treatment with excess trifluoroacetic acid, the acyl hydrazine was oxidised with NBS in THF/H_2O to give the acid and high dilution macrolatamisation with HATU/NEM provided compound **168**. In this macrolactamisation, a solution of hexapeptide **167** (1 eq) and NEM (13.5 eq) in dry CH_2Cl_2 (0.0008 M) was added dropwise to an ice-cold solution of HATU in dry CH_2Cl_2 (0.0008 M). After the addition, the reaction mixture was warmed to rt, stirred for 48 h and concentrated *in vacuo*. Cyclodepsipeptide **168** was obtained after an acid/base work-up and purification by SiO_2 flash chromatography. The product appeared as 2 inseparable spots. The only way to confirm the structure of the cyclodepsipeptide was to use mass spectroscopy. The FAB HRMS spectrum of **168** contained the appropriate $(M+Na)^+$ peak at m/e 1164.39772 (Calcd for $C_{55}Cl_3H_{70}N_7NaO_{13}$ $(M+Na)^+$ 1164.39946). The Troc group was then detached with Zn dust in aqueous acetic acid,

and the crude amine immediately capped with a Z-group using benzylchloroformate and 10% aqueous $NaHCO_3$. The product appeared again as 2 inseparable spots after purification by silica gel flash chromatography and the structure was confirmed by mass spectroscopy analysis. Cyclodepsipeptide **169** shows the appropriate $(M+Na)^+$ peak at m/e 1124.52750 (Calcd for $C_{60}H_{75}N_7NaO_{13}$ $(M+Na)^+$ 1124.53203). Hydrogenation over Pd/C in the presence of one equivalent of HCl in MeOH provided the final cyclodepsipeptide **13** as a yellow powder.



Scheme 37. Synthesis of an L-proline analogue of GE3 cyclodepsipeptide **13**

^{1}H and ^{13}C NMR spectra of cyclodepsipeptide **13** in MeOD are shown in Figure 8 and 9.

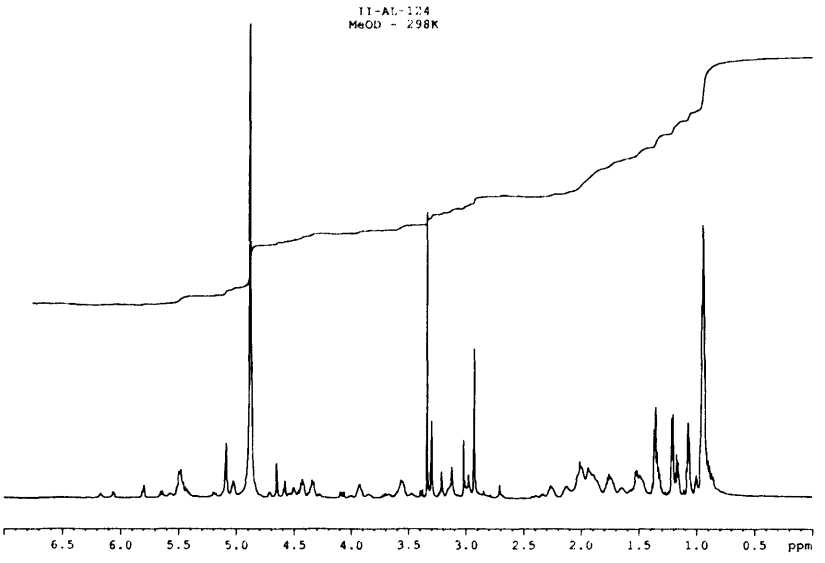


Figure 8. ^{1}H NMR spectrum of cyclodepsipeptide **13** in MeOD

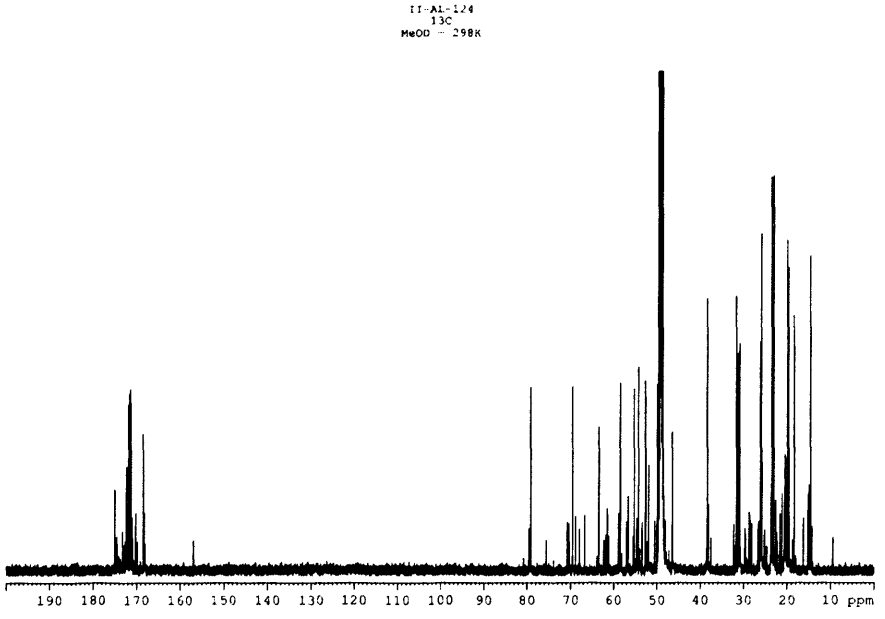


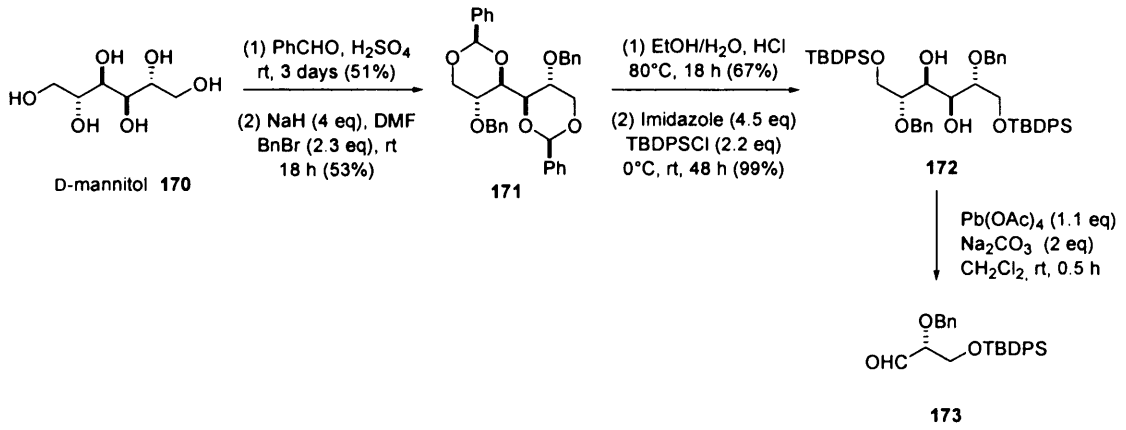
Figure 9. ^{13}C NMR spectrum of cyclodepsipeptide **13** in MeOD

These NMR spectra hinted that the formation of the desired cyclodepsipeptide occured. However ^{13}C NMR spectrum shows that the product **13** is not pure. As it is very difficult to purify

a salt, a more careful purification will have to be carried out at an earlier stage. Indeed all effort to purify the mixture obtained for compound **169** by SiO_2 flash chromatography and preparative chromatography failed.

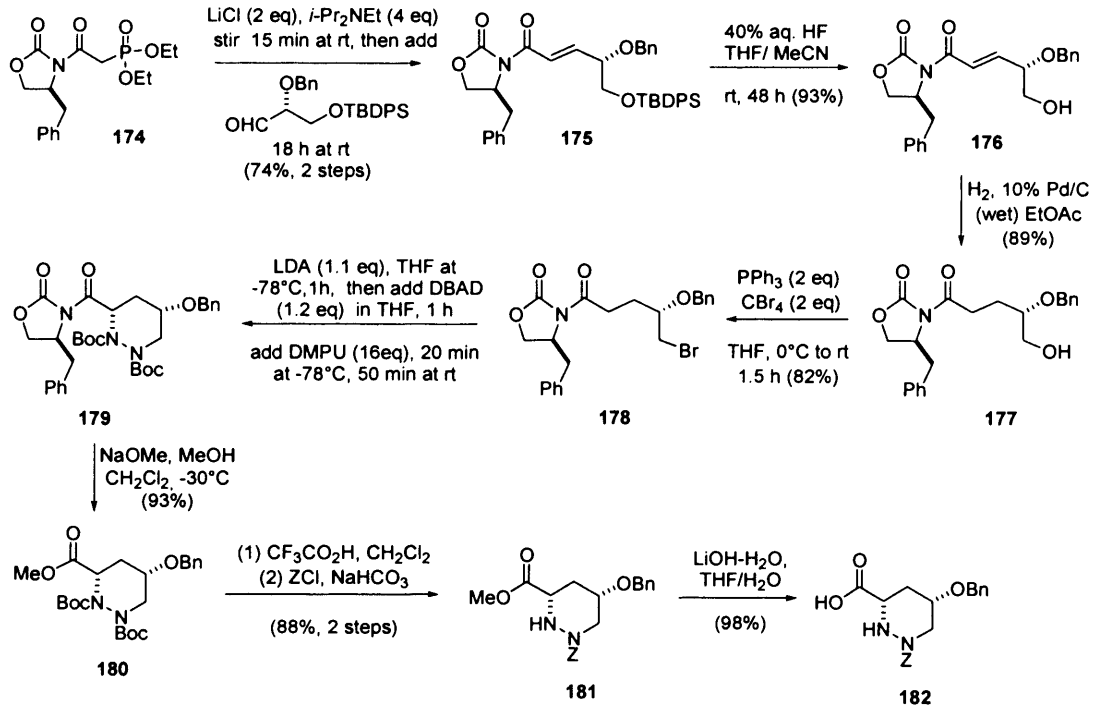
3.2. Toward the synthesis of an (3S, 5S)-5-hydroxypiperazic acid modified mimetic of A83586C

The retrosynthetic plan of the cyclodepsipetide analogue of A83586C incorporating a (3S, 5S)-5-hydroxypiperazic acid **14** was described earlier in this section (Scheme 29). Since dipeptides **64** and **66** has already been synthesised, our attention focused on the formation of compound **156** which contains the (3S, 5S)-5-hydroxypiperazic acid moiety. The desired protected form of hydroxypiperazic acid was synthesised following a procedure developed in our lab[38] (Scheme 38 and 39). The synthesis commenced with a regioselective protection of D-mannitol **170** as shown in Scheme 38.[39] First, protection of 1,3-diols occurred with benzaldehyde and conc. H_2SO_4 in dry DMF for 4 days. The reaction had to be quenched very slowly with saturated aqueous $NaHCO_3$ because of liberation of gas. The resulting diol was protected with benzylbromide and sodium hydride in dry DMF to give **171**. Compound **171** was then hydrolysed with conc. HCl in MeOH and water. After neutralisation of the reaction mixture with 20% aq. $NaHCO_3$ and extractive work-up with EtOAc, the resulting tetrol **172** was selectively protected with TBDPSCl and imidazole. Diol **172** was obtained as the single product and was cleaved with $Pb(OAc)_4$ in CH_2Cl_2 to give aldehyde **173**.



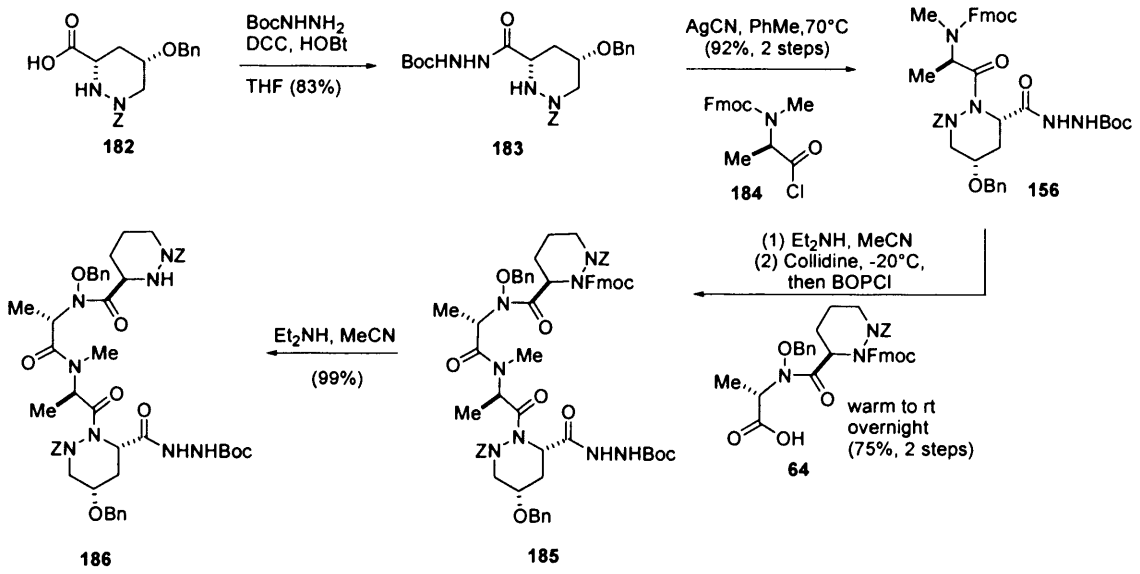
Scheme 38. Formation of aldehyde **173**

Aldehyde **173** was condensed with known phosphonate **174**[40] in a Wittig-Horner olefination to furnish alkene **175**. This reaction took place under Roush-Masamune conditions[41], i.e. in the presence of lithium chloride and diisopropylamine; Li^+ form a complex with the carbanion derived from the phosphonate. Desilylation was next performed with 40% aq. HF to afford alcohol **173** in 93% yield. A carefully monitored hydrogenation allowed chemoselective reduction of the the olefin. The hydrogenated product **177** move slightly slower than alkene **176** on TLC. The more polar product visible on TLC is the debenzylated product. The resulting alcohol **177** was converted to bromide **178** using PPh_3 and CBr_4. The piperazic unit was then elaborated by delivery of di-*tert*-butylazodicarboxylate to the lithium enolate of compound **178**. This highly stereoselective hydrazination took place only when DMPU was added to the reaction mixture and proceeded in 58% yield. The chiral auxiliary was cleaved with sodium methoxide in 93% yield to give methyl ester **180**. The Boc protective group was removed with TFA in CH_2Cl_2, and the crude TFA salt was selectively protected using benzylchloroformate in aq. $NaHCO_3$. Hydrolysis of ester **181** with $LiOH\text{-}H_2O$ produced hydroxy-piperazic acid derivative **182** in 98% yield. It is noteworthy that using this procedure, we were able to produce 20 g of intermediate **182**.



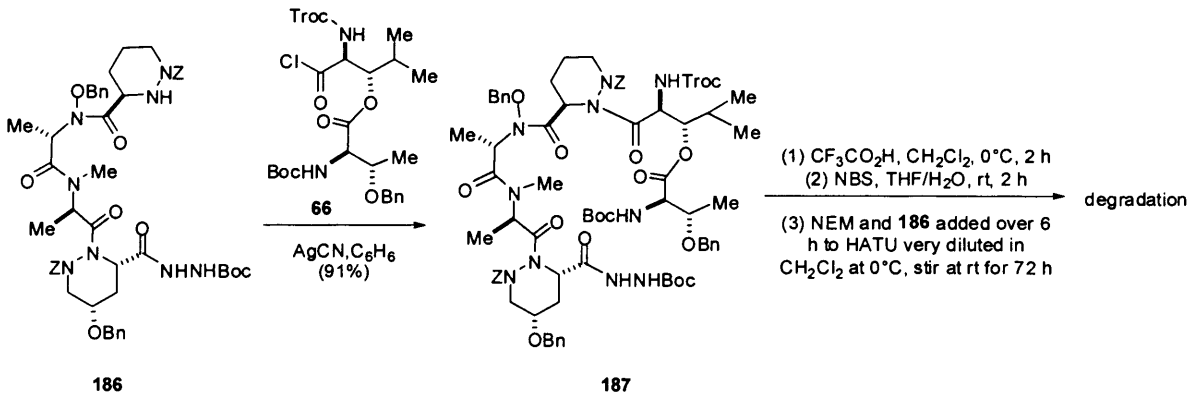
Scheme 39. Synthetic route to hydroxypiperazic derivative **182**

Acid **182** was converted to compound **183** using *t*-butylcarbazate in the presence of DCC and HOBt (Scheme 40). Subsequent coupling of acyl hydrazine **183** with Fmoc-*N*-methyl-D-alanoyl chloride **184** in benzene at 80 °C using silver cyanide as a promoter proceeded in 92% yield. After cleavage of the Fmoc group under standard conditions, the [2+2] coupling was conducted at -20 °C using BOPCl as a coupling reagent and collidine as a base. Tetrapeptide **185** was obtained as a white foam in 68% yield over 2 steps. The structure of compound **185** was confirmed by FAB HRMS analysis which showed a $(M+Na)^+$ peak at m/e 1237.52395 (Calcd for $C_{67}H_{74}N_8NaO_{14}$ $(M+Na)^+$ 1237.52219). The ^1H NMR and ^{13}C NMR spectra displayed very broad peaks due to the presence of rotamers. Eventually cleavage of the Fmoc group provided compound **186** in 99% yield.



Scheme 40. Formation of tetrapeptide **186**

Coupling of the deprotected tetrapeptide **186** with acid chloride **66** was performed using silver cyanide as shown in Scheme 41.



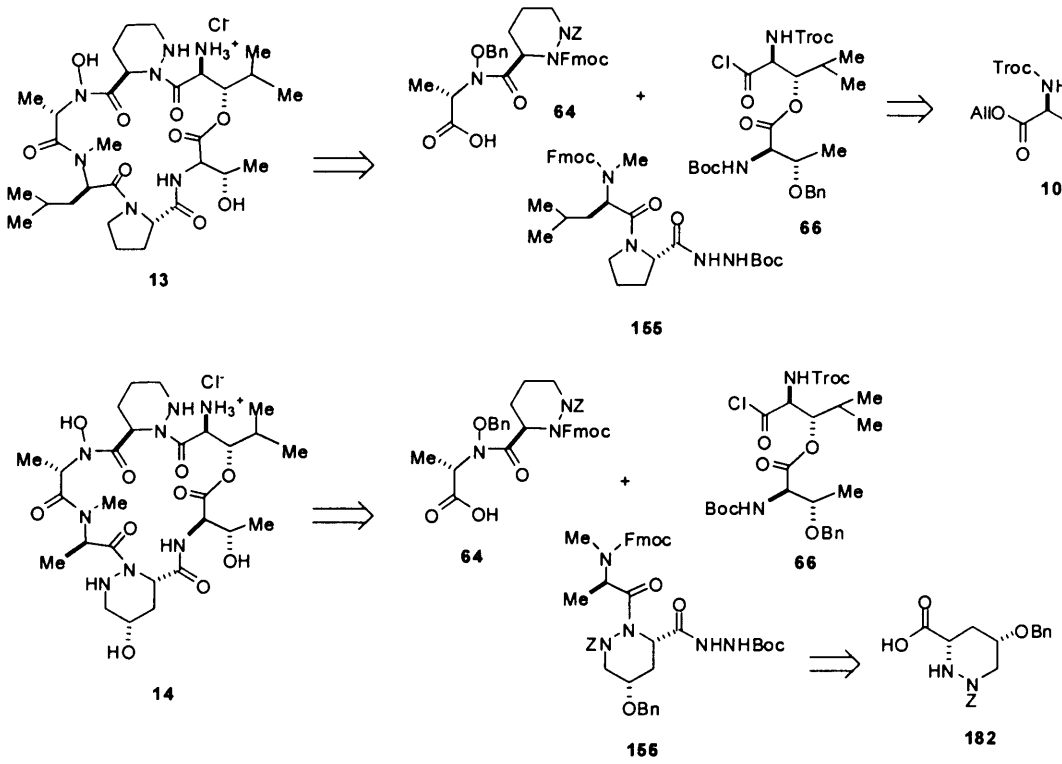
Scheme 41. Formation of hexapeptide **187** and attempt of macrolactamisation

TLC analysis of the crude mixture showed the formation of 2 compounds. After separation by silica gel flash chromatography, two compounds were isolated in 43% and 48% yield respectively. FAB HRMS analysis showed a $(M+Na)^+$ peak at m/e 1609.59520 and a $(M+Na)^+$ peak at m/e 1609.59929. These two compounds showed a $(M+Na)^+$ peak that matched the theoretical mass of hexapeptide **186** (Calcd $(M+Na)^+$ for $C_{77}Cl_3H_{97}N_{10}NaO_{20}$: 1609.58436).

It can be speculated that the [4 + 2] condensation gave rise to diastereoisomers; some epimerisation had occured. Nevertheless, we decided to carry out the 3 steps macrolactamisation procedure on both compounds separately. For both reactions, TLC analysis showed the formation of at least five compounds, and no pure product could be isolated from the reaction mixtures. Unfortunately hexapeptide **186** was all used up in this last reaction. Therefore, the macrolactamisation could not be repeated.

4. Conclusion

Our initial aim of this work was to achieve the total synthesis of two new cyclodepsipeptide rings; the proline analogue cyclodepsipeptide of GE3 **13** and the (3S,5S)-5-hydroxypiperazic acid analogue cyclodepsipeptide of A83586C **14**. These syntheses were based on a [2+2+2] coupling of three dipeptides (Scheme 42). Dipeptide **64** and depsipeptide **66** were synthesised using procedures previously developed in our lab and large amount (40g) of protected (2*S*,3*S*)-3-hydroxyleucine **109**, precursor of **66** were prepared. Furthermore, intermediates **155** and **156** were successly prepared. Intermediate **155** was prepared in 8 steps and 36% overall yield from L-proline and D-leucine. Intermediate **156** was synthesised in 24 steps and <0.04% yield from commercially available starting materials. 20 g of protected (3S,5S)-5-hydroxypiperazic acid **182** were prepared.



Scheme 42.

Cyclodepsipeptide **13** was prepared but it could not be purified. Further investigation would have been needed to confirm the formation of **13** and develop a procedure to access the pure form of **13**. Furthermore, degradation occured at the macrolactamisation step of the synthesis of cyclodepsipeptide **14**. Again further work would have been required to find a way to close the cyclodepsipeptide ring.

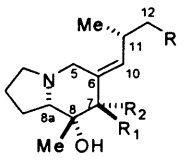
However, we learnt at that time that Novartis no longer wished to test the proposed analogues. We thus decided that it was not worth starting again the multistep synthesis of some precursors that were missing to pursue the investigation. We therefore changed programme and decided to start investigating the total synthesis of (+)-allopumiliotoxin 339A.

PART B: SYNTHETIC STUDIES TOWARDS THE SYNTHESIS OF (+)-ALLOPUMILIOTOXIN 339A

5. Introduction

5.1. Isolation of the Pumiliotoxin A and the Allopumiliotoxin alkaloids

A wide range of lipophilic alkaloids are present in the skin of amphibians.[42] The pumiliotoxin A and allopumiliotoxin classes of alkaloids are a major group of alkaloids of general structure **187** (Figure 10). The pumiliotoxin A alkaloids have R_1 = R_2 = H whereas the allopumiliotoxins have a 7-hydroxy substituent on the indolizidine ring (R_1 or R_2 = OH). The allopumiliotoxins are the most complex members of this class of alkaloids and are present in *Dendrobatid* frogs in a small quantity.



187

pumiliotoxin A alkaloids : R_1 = R_2 = H
allopumiliotoxin alkaloids : R_1 = H, R_2 = OH
or R_1 = OH, R_2 = H

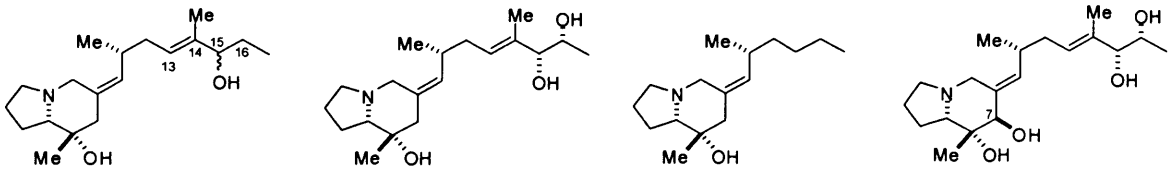
Figure 10. General structure of the pumiliotoxin family of alkaloids

The pumiliotoxin alkaloids were originally believed to be unique to Dendrobatid frogs, however they are now known to be present in virtually all anurans that are chemically defended by the presence of lipophilic alkaloids.[43,44] The pumiliotoxins appear to be derived from dietary sources[45], such as ants and arthropods. Recently the pumiliotoxins 307A and 323A were detected in extracts of formicine ants[46], other pumiliotoxins (237A and 251D) were found in oribatid mites.[47] Furthermore, it has been recently shown that dendrobatid frogs have an

enzyme, pumiliotoxin 7-hydroxylase that can convert a dietary pumiliotoxin to a more toxic allopumiliotoxin.[48]

In 1967, pumilotoxin A (327A) and pumiliotoxin B (323A) were the first molecules of the family to be isolated by Daly and co-workers, from the brightly colored Panamanian poison frog *Dendrobates pumilio*.[49] The structures of these pumiliotoxins remained unknown until 1980 when X-ray analysis of the crystalline hydrochloride salt of pumiliotoxin 251D established the structure and absolute configuration of this alkaloid.[50] Analysis by mass spectroscopy and NMR allowed the elucidation of the structures of other members of the family.[50,51] Figure 11 shows the structure of some pumiliotoxin alkaloids.

Allopumiliotoxin 339A **191** was isolated, along with its isomer, allopumiliotoxin 339B, in skin extracts of *Dendrobates auratus* in 1984.[51] Allopumiliotoxin 339A differs from 339B in the stereochemistry of the hydroxyl group at C(7). Allopumiliotoxin 339A and 339B had been first detected in 1978 and had been incorrectly classified as the alkaloid 395, due to the fact that they were converted to a dimethylsilanate during gas chromatography analysis.[52] They represent minor alkaloids in these Dendrobatid frogs. The allopumiliotoxins 339 are the hydroxyl congeners of pumiliotoxin B.



Pumiliotoxin A **188** Pumiliotoxin B **189** Pumiliotoxin 251D **190** Allopumiliotoxin 339A **191**

Figure 11 : Structure of some pumiliotoxin alkaloids

5.2. Biological Properties of the Pumiliotoxins

The dendrobatids frogs are notoriously toxic; the native people of Western Columbia use skin secretions from three species of these frogs to poison the darts used in hunting. The pumiliotoxin family of alkaloids exhibit potent cardiotonic and myotonic activities.

5.2.1. Ion Channels and the Electrical Properties of Membranes

Ion channels are proteins that form hydrophilic pores across plasma membranes of cells (Figure 12). Most of the ion channels exist in either an open or a closed conformation, and are said to be gated. The main types of stimuli that are known to cause ion channels to open are the binding of a ligand (ligand-gated channels) or a change of the voltage across the membrane (voltage-gated channels).

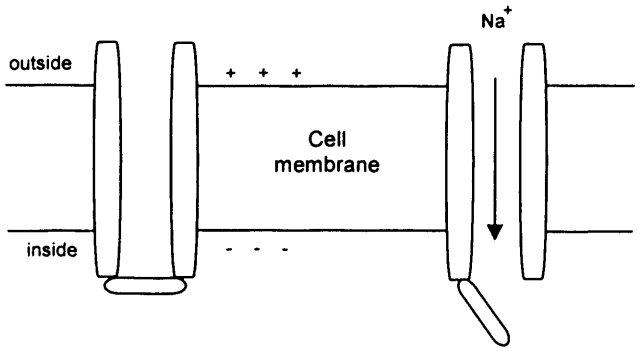


Figure 12. Voltage gated sodium channels

A voltage gradient, also called an electric potential exists across the plasma membrane of all cells, the inside of the cell is negative relative to the outside. This potential across the membrane at rest is called the resting potential and is between -30mV and -70 mV. When the cell is at rest, anions give it a negative charge, with sodium ions outside and potassium ions inside the cell. In most animal cells, this potential does not vary with time. However, neurons and muscles cells, which are electrically active cells, undergo changes in their membrane potential.

When changes occur in the membranes, the voltage-gated sodium channels respond to allow sodium ions to enter thereby, balancing the charge. When this occurs the membrane potential becomes less negative and more sodium channels open, causing an even greater influx of sodium ions. When the membrane potential reaches around +30 mV, the gates of the sodium channels close and the voltage-gated potassium channels begin to open. The sodium channel remains unactivated for a few milliseconds, such that no further sodium ions can enter the cell from that gate.

This occurs at one little segment of the axon at a time: sodium ions go in at section one; which triggers the efflux of potassium ions to start at section one and the influx of sodium ions at section two. That, in turn, triggers potassium ions to exit at section two and sodium ions to enter at section three; and so on along the membrane (Figure 13).

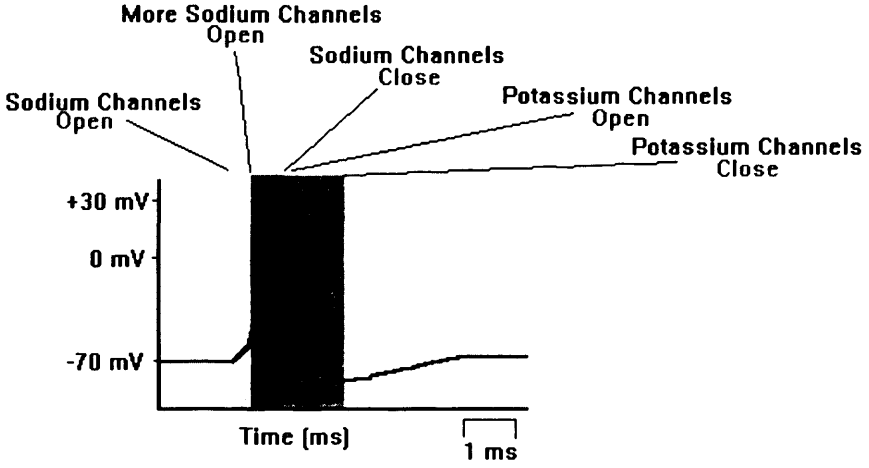


Figure 13. An action potential

An action potential results from the sequential opening and closing of voltage-gated cation channels and propagates along the cell. In conclusion, voltage-gated sodium channels are responsible for the generation and conduction of action potentials along the membrane and a transmission of a signal from one end of the cell to the other.

5.2.2. Phosphoinositide Breakdown

A variety of natural products that can affect voltage-dependent sodium channels were found to stimulate the phosphoinositide breakdown in brain synaptoneurosomes. Daly *et al.* have shown that modulation of sodium ion or sodium channel causes phosphatidylinositol turnover. However, the mechanism involved in this process is still unclear.[53] Phosphatidylinositol is a class of phospholipid, made up of glycerol, fatty acids and a hexahydric alcohol, inositol (Figure 14).

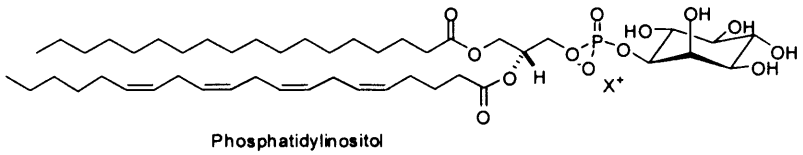
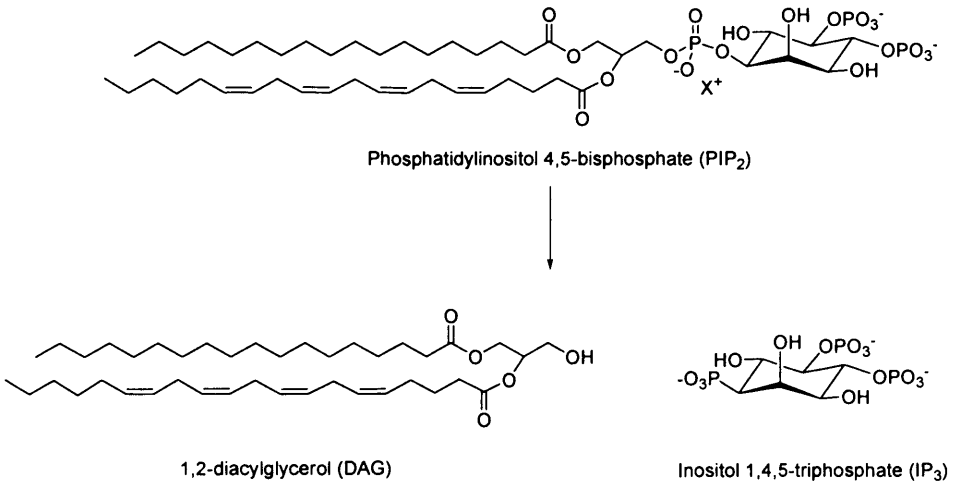


Figure 14. Phosphatidylinositol (PI)

Phosphatidylinositol is especially abundant in brain tissue, where it can amount to 10% of the phospholipids, but it is present in all tissues and cell types. Phosphatidylinositol is phosphorylated by a number of different kinases that place the phosphate moiety mainly on positions 4 and 5 of the inositol ring (PIP_2). Cleavage of phosphatidylinositol phosphates leads to generation of secondary messengers, 1,2-diacylglycerol (DAG), a lipophilic molecule that remains linked to the membrane, and free phosphorylated inositols (IP_3), which can diffuse into the cytosol (Scheme 43). Diacyglycerols regulate the activity of a group of at least a dozen related phosphorylating enzymes known as protein kinase C which, in turn, control many key cellular functions, including differentiation, proliferation, metabolism and apoptosis. The various inositol phosphates appear to be involved in the control of cellular events in very specific ways; for example, inositol 1,4,5-trisphosphate is an important cellular messenger stimulating calcium ion release from the endoplasmic reticulum.



Scheme 43. Phosphoinositide breakdown

5.2.3. Biological Activity of Pumiliotoxin Family of Alkaloids

Pumiliotoxin B (PTX-B) and some of its congeners have marked myotonic and cardiotonic activities. In nerve-striated muscle preparations, PTX-B increases direct and indirect elicited twitch. In guinea pig ileum segments, PTX-B caused rhythmic contractures which were suppressed by tetrodotoxin, a specific antagonist of the sodium potential channel.[54] This activity is due to interaction of PTX-B with a site on the voltage dependant sodium channel in synaptoneurosomes.[55] It results in a delay in inactivation of the sodium channel and repetitive firing in nerve and muscle. The resultant influx of sodium will cause activation of phosphatidylinositols thereby generating two second messengers, the inositols phosphates (which can mobilize calcium ions) and the diacylglycerols (which activate protein kinase C).[53] In neuroblastoma cells, PTX-B and active congeners had no effect on sodium flux unless synergized by a scorpion venom.[56] The pumiliotoxin binding site on voltage-dependant sodium channel appears to be allosterically coupled to the scorpion venom site.[55] Biological activity of various pumiliotoxins was initially evaluated by measuring the force and the rate of spontaneous contractions in guinea pig atrial preparations,[57] and later, the phosphoinositide breakdown and the sodium influx in synaptoneurosomes.[58,59]

5.2.4. Structure-Activity Relationship

The structures of the pumiliotoxin alkaloids discussed are drawn in Figure 15

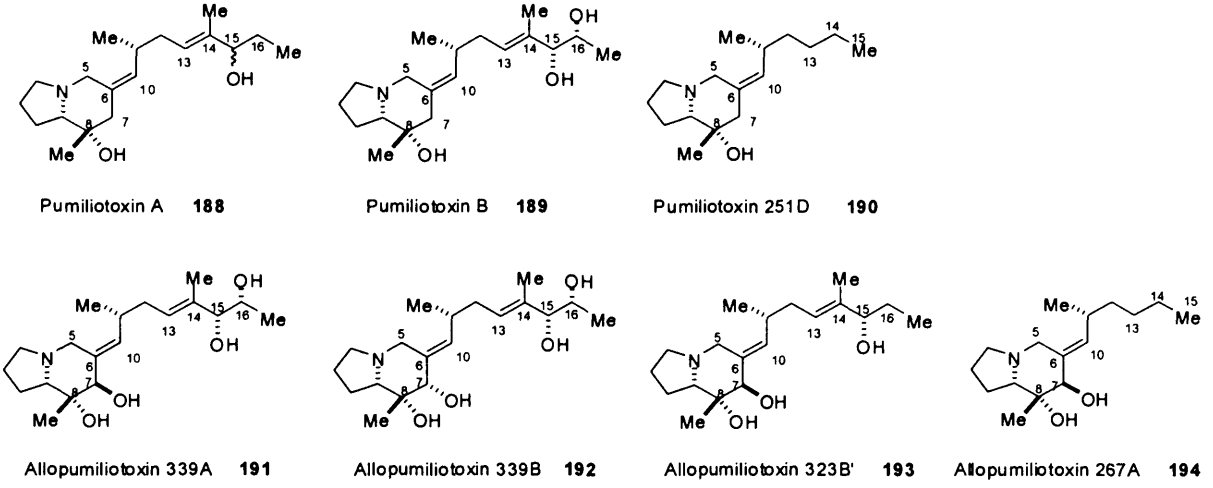


Figure 15. Members of the pumiliotoxin family of alkaloids

Pumiliotoxin B **189** is the most potent and efficacious of the compounds tested with respect to its chronotropic (rate) and inotropic (force) effects in guinea pig atrial preparations. It causes at 6 μM a 3 fold increase in force and a 2-fold increase in the rate of contractions. The nature of the side chain is critical for the biological activities of pumiliotoxins. In pumiliotoxin A **188**, the lack of the side chain C16-hydroxy group results in a reduction in activity. The absence of both C15 and C16 hydroxy groups yields cardiodepressant compounds. However, in allopumiliotoxins, the number of hydroxy groups on the side chain does not change the activity. Allopumiliotoxin 323B' **193**, the allo(C-7-hydroxy)pumiliotoxin of pumiliotoxin A, is as active as allopumiliotoxin 339A **191**. In conclusion, at least three hydroxyl groups appear to be required for high cardiotonic activity. The 7-hydroxy group on the indolizidine ring must also be axial for high cardiotonic activity; allopumiliotoxin 339B **192** is significantly less active than allopumiliotoxin 339A **191** and pumiliotoxin B **189**. Allopumiliotoxin 339A is as potent as PTX-B, with respect to rate of contractions (150% of control at 6 μM) but less efficacious with respect to the force (160% of control at 6 μM).[57,58]

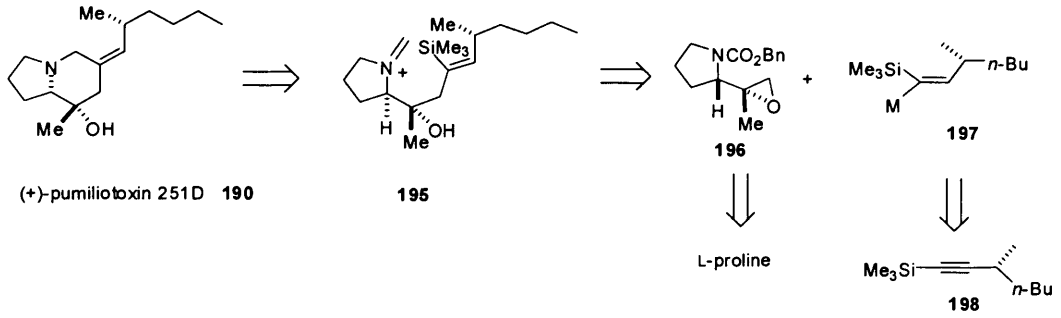
The structure-activity profile for stimulation of sodium flux and phosphoinositide breakdown by pumiliotoxins is very similar to the cardiotonic activity.[56] Allopumiliotoxin 339A is the only alkaloid of the pumiliotoxin family to be more effective than pumiliotoxin B in stimulating

sodium influx (120% of response to PTX-B) and phosphoinositide breakdown (110% of response to PTX-B). Indeed, in guinea pig cerebral cortical synaptoneurosomes, the percent of control of phosphoinositide breakdown is 280% for PTX-B at 10 μM compared to 304% for Allo-PTX 339A at the same concentration.[58]

5.3. Past syntheses of Some Members of the Pumiliotoxin Family of Alkaloids

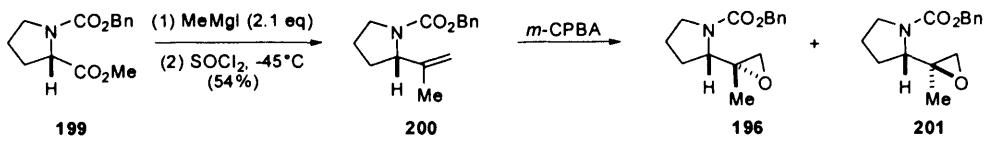
5.3.1. First Synthesis of a Pumiliotoxin A Alkaloid

The first total synthesis of a pumiliotoxin A alkaloid was reported by Overman and Bell in 1981.[60] They achieved an enantiospecific synthesis of pumiliotoxin 251D **190** using an iminium ion-vinylsilane cyclisation to stereospecifically assemble the (*Z*)-6-alkylideneindolizidine ring system (Scheme 44). The cyclisation precursor **195** would be obtained from the L-proline-derived epoxide **196** and the vinyl nucleophile **197**.



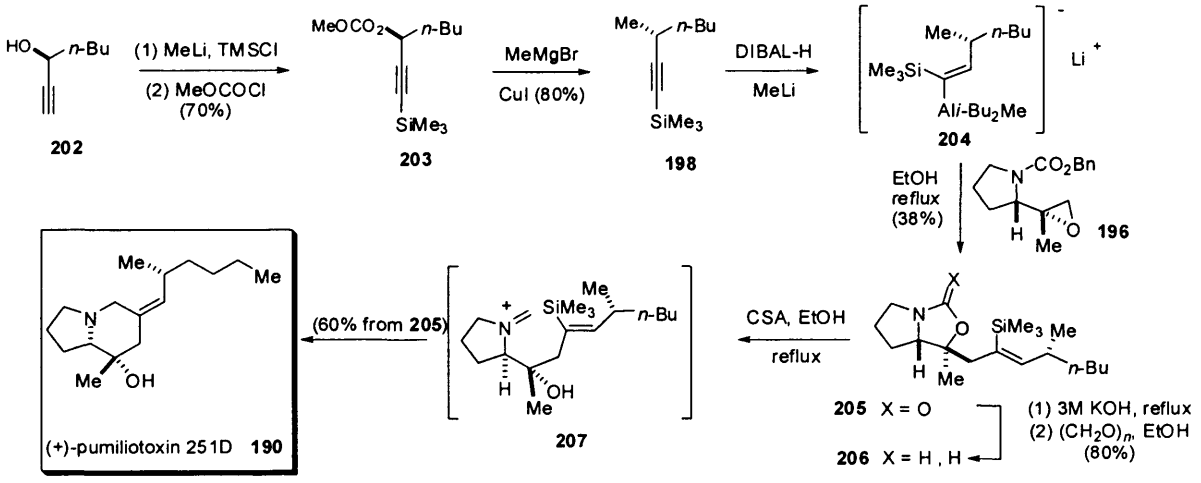
Scheme 44. Overman's first retrosynthetic plan to pumiliotoxin 251D

A non-stereoselective route was developed to access epoxide **196** from L-proline. Reaction of *N*-carbobenzyloxy-L-proline methyl ester **199** with MeMgI, followed by dehydration of the resulting tertiary alcohol with thionyl chloride afforded the propenyl derivative **200** in 54% yield. Epoxidation with *m*-CPBA gave in quantitative yield a 1:1 mixture of epoxides **196** and **201** that could be easily separated on a large scale (Scheme 45).



Scheme 45. Preparation of epoxides **196** and **201**

Elaboration of the side chain of (+)-pumiliotoxin 251D started with the reduction of 1-heptyne-3-one with *B*-3-pinanyl-9-borabicyclo[3.3.1]nonane into (*S*)-1-heptyn-3-ol **202**. Conversion into silyl carbonate **203** followed by organocuprate coupling provided stereospecifically the (*R*)-silyl akyne **198** in 56% yield from alcohol **202**. After treatment of alkyne **198** with DIBAL-H, the resulting vinylalanate **204** was heated at reflux with epoxide **196** to afford bicyclic carbonate **205** in 38% yield. Compound **205** was hydrolysed into the aminoalcohol, which was directly converted to the cyclopentaoxazolidine **206** with paraformaldehyde. The cyclisation was achieved by heating **206** in ethanol in the presence of camphorsulfonic acid (Scheme 46).

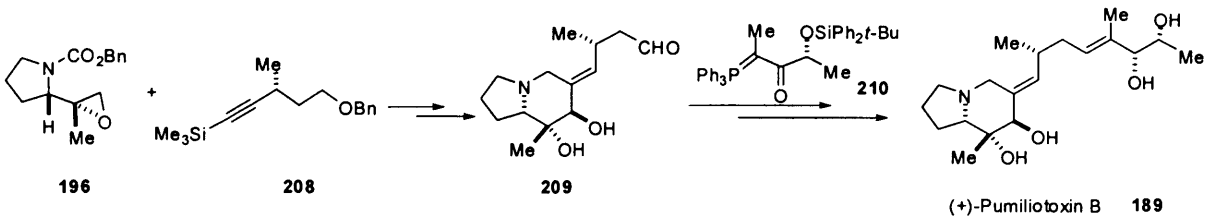


Scheme 46. Overman's route to (+)-pumiliotoxin 251D **190**

This first total synthesis of a pumiliotoxin A alkaloid proceeded in 13% yield from (*S*)-1-heptyn-3-ol and 4.7% yield from *N*-carbobenzyloxy-L-proline methyl ester. Iminium ion-

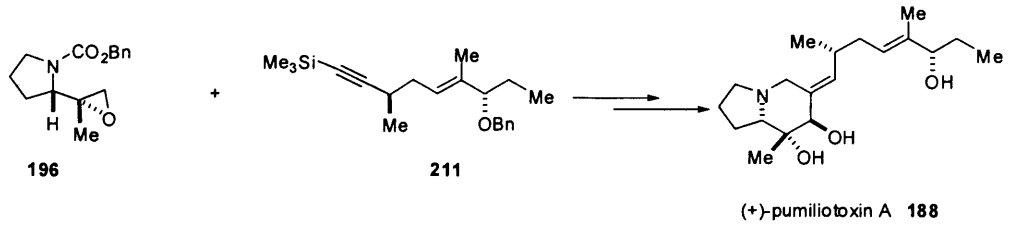
vinylsilane cyclisation was developed in this synthesis. This methodology was used in the total syntheses of pumiliotoxin B **189** in 1984[61] and pumiliotoxin A **188** in 1985.[62]

The synthesis of pumiliotoxin B **189** is summarised in Scheme 47. At the time this retrosynthetic plan was designed, the stereochemistry of the allylic diol of (+)-pumiliotoxin B **189** was still unknown. The strategy adopted allowed access to any of the four possible diastereoisomers. Iminium ion-vinylsilane cyclisation was used to obtain alkylideneindolizidine aldehyde **209** which was condensed with stabilised ylide **210** to provide (+)-pumiliotoxin B **189**.



Scheme 47. Preparation of (+)-pumiliotoxin B **189** using iminium ion-vinylsilane cyclisation

Using the same methodology, (+)-pumiliotoxin A was synthesised from epoxide **196** and vinylalanate of **211** (Scheme 48).

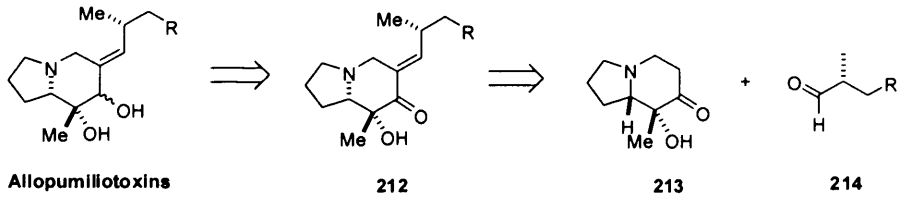


Scheme 48. Preparation of (+)-pumiliotoxin A **188** using iminium ion-vinylsilane cyclisation

In theses 3 syntheses, low yields were obtained in the epoxide-alanate coupling step requiring optimisation for each side chain nucleophile. A more efficient strategy had to be designed in order to synthesise larger amounts of the compounds necessary for investigation of the biological activities of the pumiliotoxin family of alkaloids.

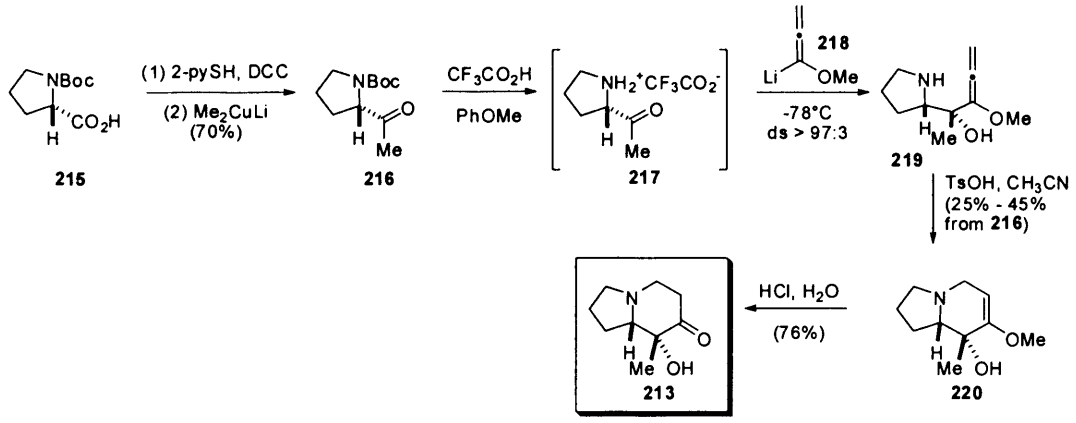
5.3.2. Overman Aldol Attachment of the Alkylidene Side Chain: First Entry to an Allopumiliotoxin Alkaloid

The first synthesis of an allopumiliotoxin A alkaloid was reported in 1984 by Overman and Goldstein.[63,64] Their method was based on an aldol attachment of the alkylidene side chain **214** to indolizidinone **213** as illustrated in Scheme 49 and was used in the synthesis of allopumiliotoxin 267A and allopumiliotoxin 339B.



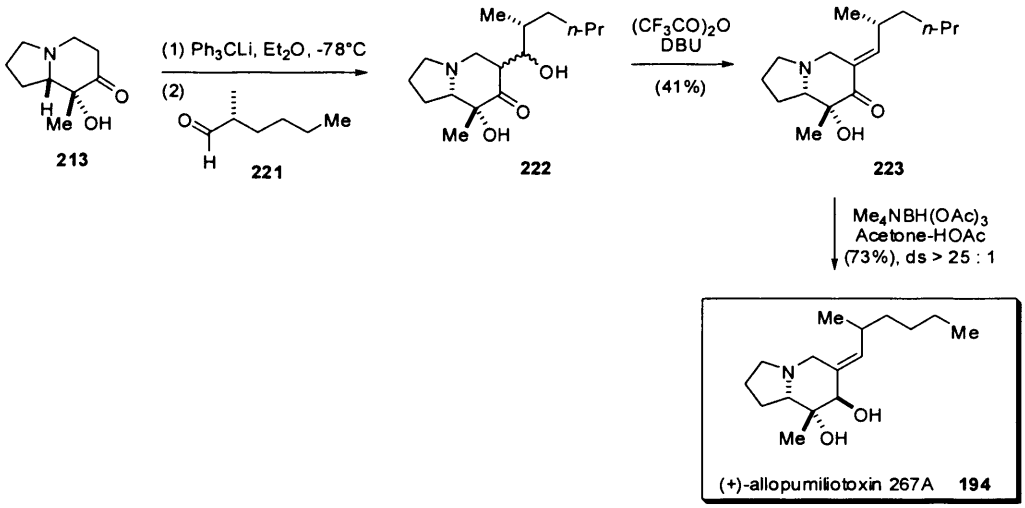
Scheme 49. Overman Aldol Attachment of the Alkylidene Side Chain

The synthesis of indolizidinone **213** started from *N*-Boc-L-proline **215** which was first converted to ketone **216** in 2 steps (Scheme 50). After deprotection with TFA, the labile 2-acetopyrrolidine salt **217** was treated with 5 equivalent of 1-lithio-1-methoxyallene **218** in THF at -78 °C to afford the allenyl pyrrolidine **219** as a single diastereoisomer. Crude **219** was reacted with slightly less than one equivalent of *p*-toluenesulfonic acid in acetonitrile to provide the bicyclic enol ether **220** in 25-45% yield from compound **216**. Conversion of enol ether **220** to the 7-indolizidinone **213** was then achieved in 76% yield by hydrolysis with 5% aqueous HCl.



Scheme 50. Synthesis of intermediate **213**

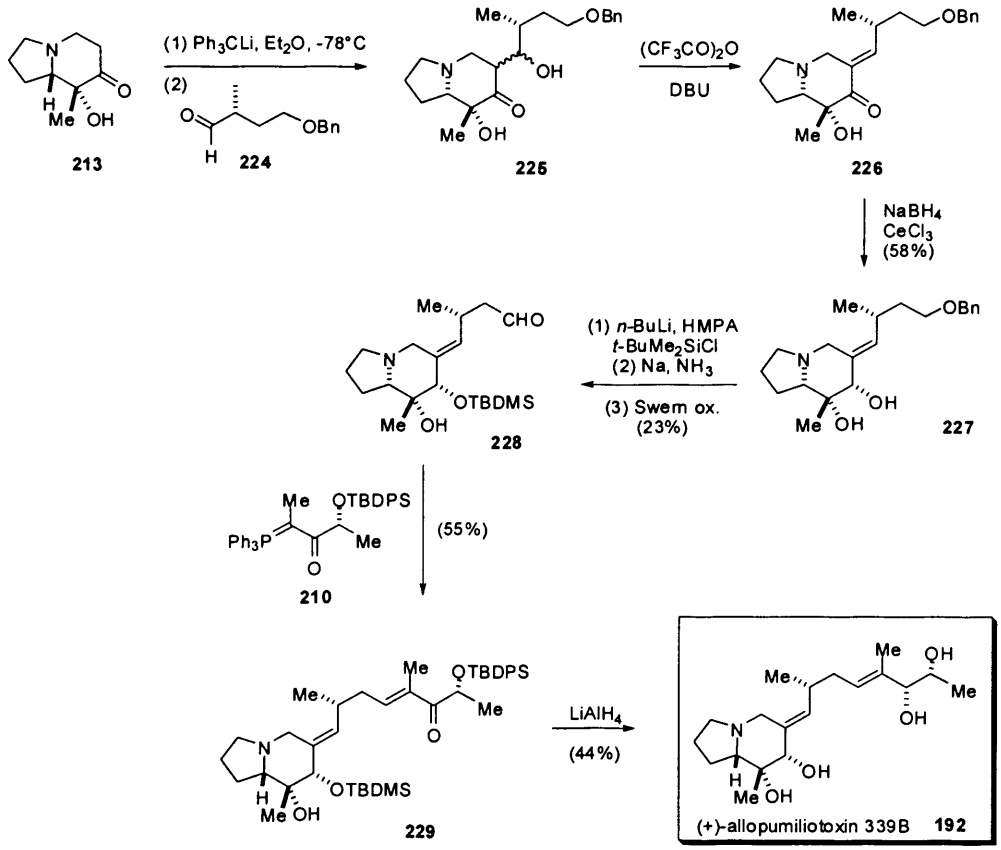
The final steps of the synthesis of (+)-allopumiliotoxin 267A **194** are shown in Scheme 51. The best result for the aldol condensation was obtained with 2 equivalent of trityllithium in ether 0°C. The aldol adduct **222** was directly dehydrated with trifluoroacetic anhydride and DBU to yield compound **223**, which was selectively reduced with $Me_4NBH(OAc)_3$ to afford (+)-allopumiliotoxin 267A **194** in 73% yield.



Scheme 51. Synthesis of (+)-allopumiliotoxin 267A **194**

Similar chemistry was utilised for the preparation of (+)-allopumiliotoxin 339B **192** as illustrated in Scheme 52. Reduction of compound **226** under Luche conditions furnished only the equatorial alcohol **227** in 58% yield. Silylation of alcohol **227** followed by debenzylation with

sodium in ammonia and Swern oxidation afforded aldehyde **228**. Wittig olefination of aldehyde **228** with enantiomerically pure ylide **210** provided the α'-silyloxy (*E*)-enone **229** in 54% yield. *Threo*-selective reduction with $LiAlH_4$ was accompanied by desilylation to afford (+)-allopumiliotoxin 339B **192** in 44% yield.

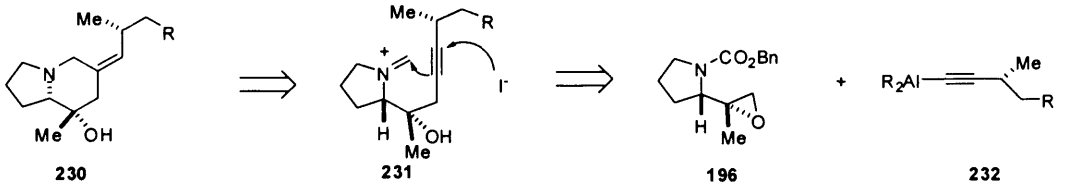


Scheme 52. Overman's route to (+)-allopumiliotoxin 339B **192**

The overall yields of these syntheses are quite low; (+)-allopumiliotoxin 267A was prepared in 9 steps and 5.6% overall yield from *N*-Boc-L-proline and (+)-allopumiliotoxin 339B was prepared in 14 steps and an overall yield <1% from *N*-Boc-L-proline. However, these syntheses allowed confirmation of the absolute configurations of these alkaloids. Moreover, this aldol dehydration strategy was also employed by Gallagher and coworkers in their synthesis of pumiliotoxin 251D.[65]

5.3.3. Total Syntheses Using Iodide-Promoted Iminium Ion-Alkyne Cyclizations

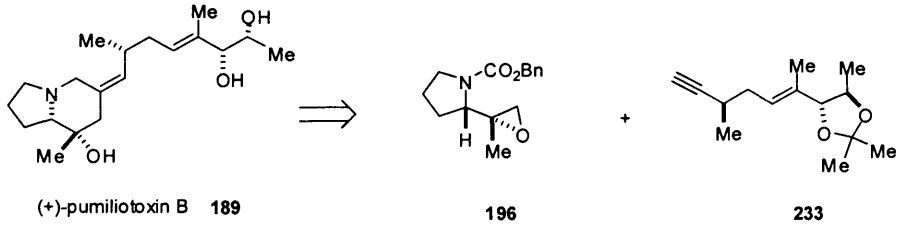
Overman *et al.* reported that alkynes can react intramolecularly with iminium ions in the presence of a nucleophile.[66] This strategy, illustrated in scheme 53, was first utilized to prepare pumiliotoxin A in 1988[67] and has later been successful for the preparation of pumiliotoxin B[68] and allopumiliotoxins alkaloids[59,69] as well as many structural analogues.[70]



Scheme 53. Preparation of pumiliotoxins using iodide-promoted ion-alkyne cyclisation

5.3.3.1. Total synthesis of Pumiliotoxin B

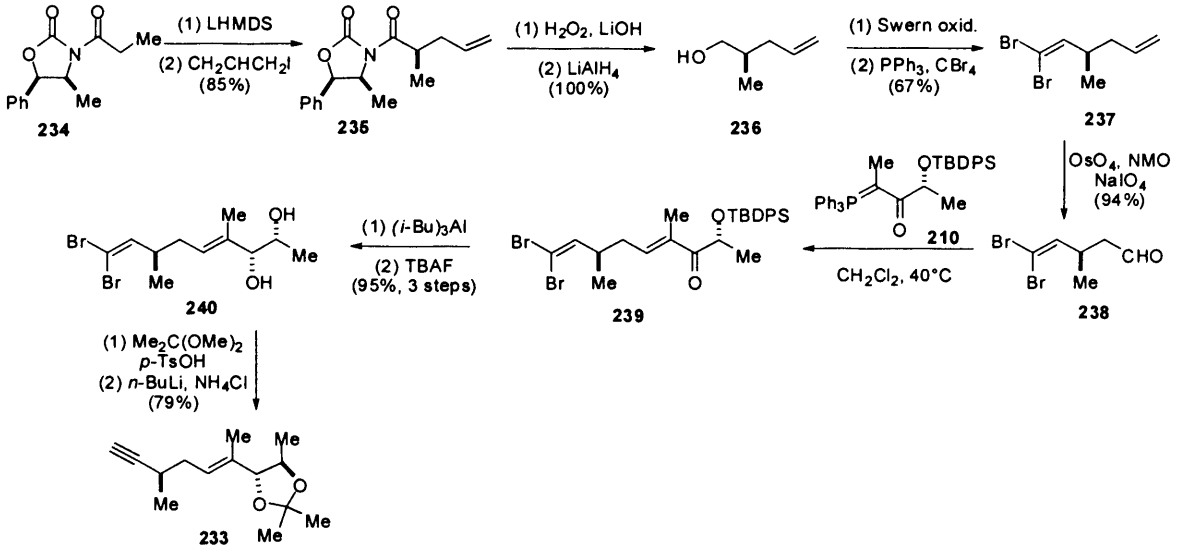
(+)-Pumiliotoxin B **189** was prepared using iodide-promoted iminium ion-alkyne cyclisation from epoxide **196** and alkyne **233** (Scheme 54).



Scheme 54. Retrosynthetic analysis of (+)-pumiliotoxin B

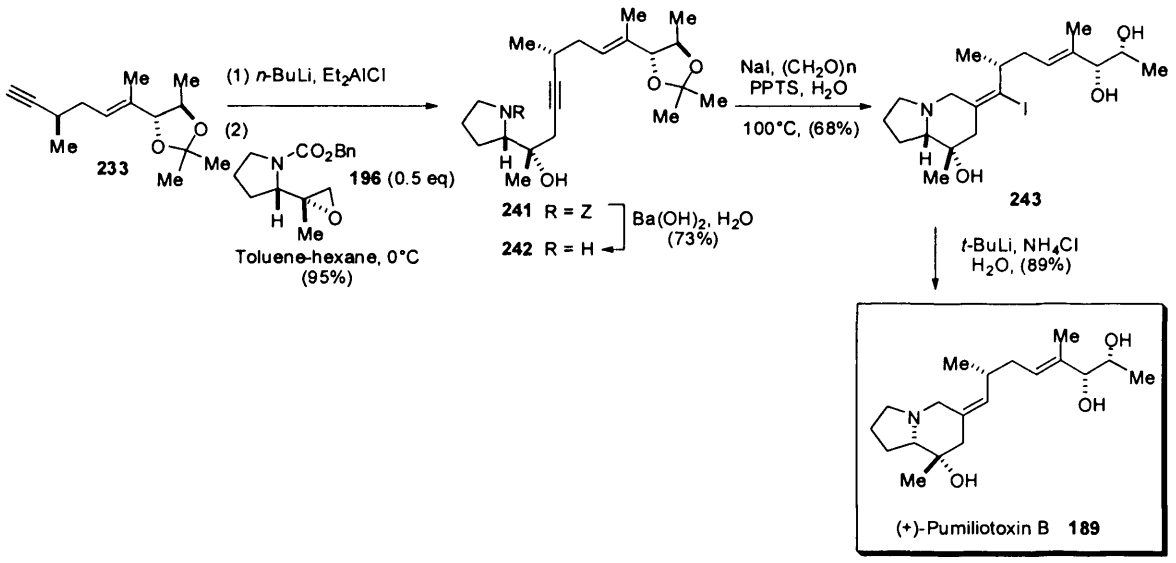
The synthesis of alkyne **233** is depicted in Scheme 55 and began with Evans allylation of propionyl oxazolidinone **234**. Removal of the auxiliary with hydrogen peroxide and $LiAlH_4$ reduction afforded (*R*)-2-methyl-4-pentenol **236**. Dibromide **237** was obtained after Swern oxidation of alcohol **236** followed by dibromomethylenation with PPh_3 and CBr_4. Wittig

olefination of aldehyde **238** with phosphorane **210** provided α-siloxyenone **239** which was selectively reduced with triisobutylaluminium. Deprotection of the silyl group afforded the *syn* diol **240** which was converted to the acetonide with 2,2-dimethoxypropane. Conversion of the dibromoalkene to the terminal alkyne **233** was achieved under standard conditions. The synthesis of alkyne **233** was achieved in 8 steps from pentanol **236** and 42% overall yield.



Scheme 55. Synthesis of the side chain segment of pumiliotoxin B

Coupling of pyrrolidine epoxide **196** with 2 equivalents of the diethylaluminium derivative of alkyne **233** proceeded efficiently to afford intermediate **241** in 95% yield (Scheme 56). In contrast to the vinylsilane route, the unreacted alkyne **233** was easily recovered allowing this key coupling step to proceed in excellent yield with net use of stoichiometric amounts of the coupling partners. The same conditions were used in the synthesis of pumiliotoxin A and analogues. Hydrolytic removal of the carbamate group with $Ba(OH)_2$ provided alkynylamine **242** in 73% yield. After optimisation, the iodide-promoted cyclisation was performed with 1.5 equiv of PPTS which resulted in both cyclisation and isopropylidene cleavage to afford compound **243** as a single isomer in 65% yield. Deiodination of **243** followed by protonolysis provided (+)-pumiliotoxin B **189** in 89% yield.

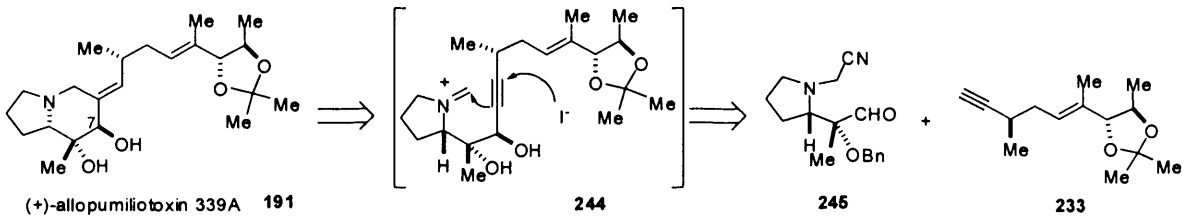


Scheme 56. Preparation of (+)-pumiliotoxin B using iodide-promoted ion-alkyne cyclisation

This synthesis allowed preparation of 500 mg of pumiliotoxin B for biological and structural investigations. The overall yield was 8% from *N*-carbobenzyloxy-L-proline and 10% from (4*S*, 5*S*)-4-methyl-5-phenyl-2-oxazolidinone, the commercially available precursor of acyloxazolidinone **234**.

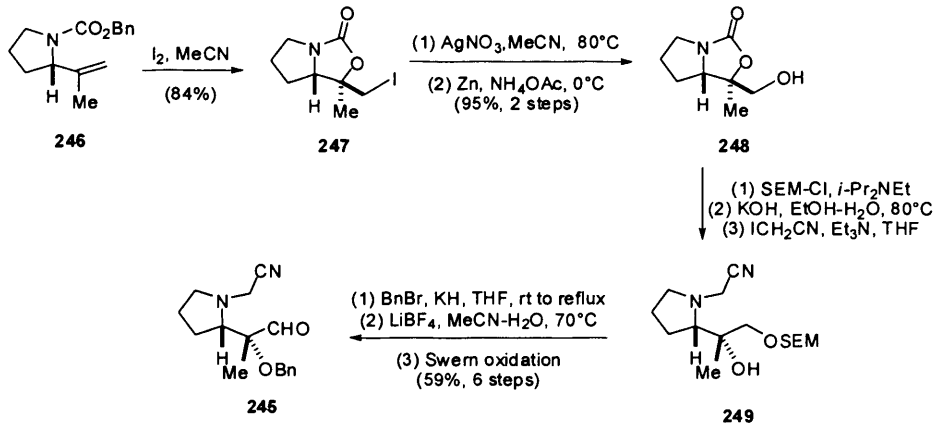
5.3.3.2. First Enantioselective Total Synthesis of (+)-Allopumiliotoxin 339A

The first total synthesis of (+)-allopumiliotoxin 339A was reported in 1992 by Overman *et al.* The general approach is outlined in retrosynthetic format in Scheme 57 and involves the coupling of the proline-derived aldehyde **245** with the terminal alkyne **233**.[69] The key issue of the synthesis was the viability of the pivotal nucleophile-promoted iminium ion-alkyne cyclisation step with a substrate that contained a potentially labile and inductively deactivating C(7) allylic hydroxyl group. This was achieved using the electron-withdrawing cyanomethyl protecting group which would disfavour competitive chelation with the pyrrolidine nitrogen during the carbonyl addition step.



Scheme 57. First retrosynthetic plan to (+)-allopumiliotoxin 339A **191**

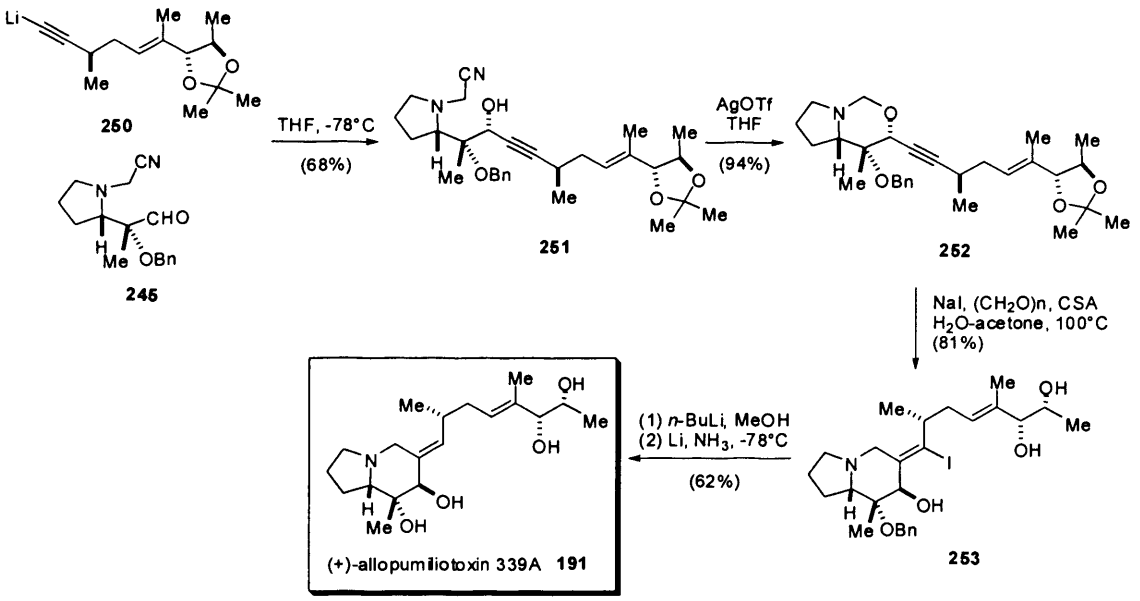
Aldehyde **245** was obtained from propenyl derivative **246** through an efficient 9 step-sequence which is depicted in Scheme 58.[71] Iodocyclisation of **246** afforded a bicyclic iodo carbamate **247** which was converted to alcohol **248** after conversion into a nitrate ester and reduction. After protection of the alcohol, the cyclic carbamate was hydrolysed with KOH and the secondary amine was protected with a cyanomethyl group to give compound **249**. Following protection of the tertiary alcohol with benzyl bromide, the primary alcohol was deprotected and oxidised under Swern conditions to afford aldehyde **245** in 45% overall yield from **246**.



Scheme 58. Synthesis of aldehyde **245**

Addition of compound **250**, the alkynyl lithium derivative of **233**, to aldehyde **245** occured in 68% yield with 4:1 diastereoselectivity in favour of **251**. A first iminium ion cyclisation by internal attack of oxygen nucleophile yielded cyclopentaoxazine **252**. Then iodide-promoted cyclisation occured cleanly at 100 °C with loss of isopropylidene group to afford

alkylideneindolizidine **253** in 76% overall yield from **251**. Deiodination followed by removal of the benzyl ether provided (+)-allopumiolliotoxin 339A **191** in 62% yield (Scheme 59).



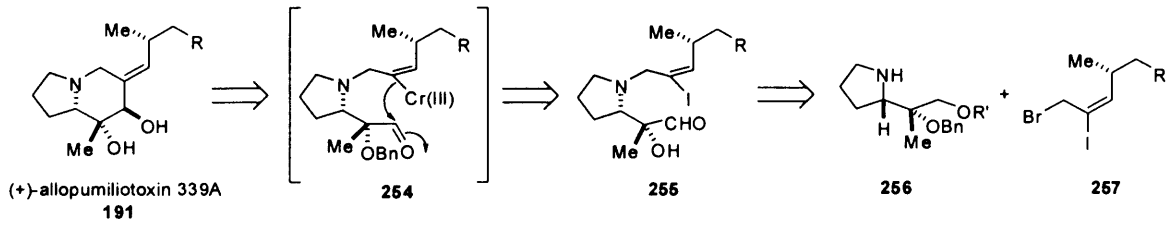
Scheme 59. First total synthesis of (+)-allopumiliotoxin 339A

This first synthesis of (+)-allopumiolliotoxin 339A proceeded in 17 steps and 7.5% overall yield from *N*-(benzyloxycarbonyl)-L-proline and 16 steps and 6% overall yield from the commercially available precursor of acyloxazolidinone **234**.

5.3.4. Alternative Strategies for (+)-Allopumioliotoxin 339A Synthesis

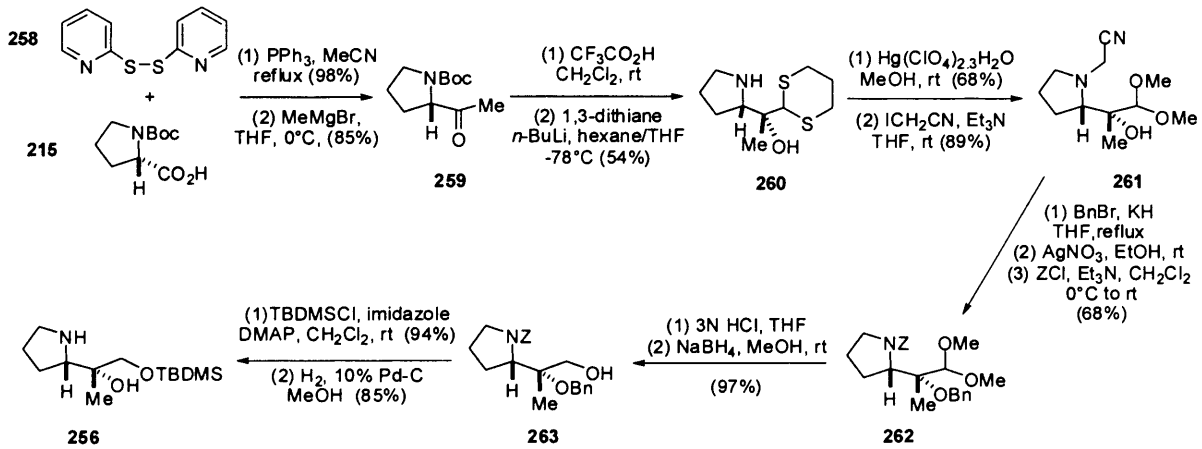
5.3.4.1. Nozaki-Kishi cyclisation

In 1992, Kibayashi and co-workers utilised an intramolecular Cr(II)-mediated coupling reaction[72,73] to build the indolizine framework of the allopumiliotoxin alkaloids.[74,75] The strategy employed is summarized in Scheme 60, the cyclisation proceeded *via* an alkenylchromium (III) species **254**. The cyclisation precursor **255** came from the combination of the protected pyrrolidine fragment **256** and allylic bromide **257**.



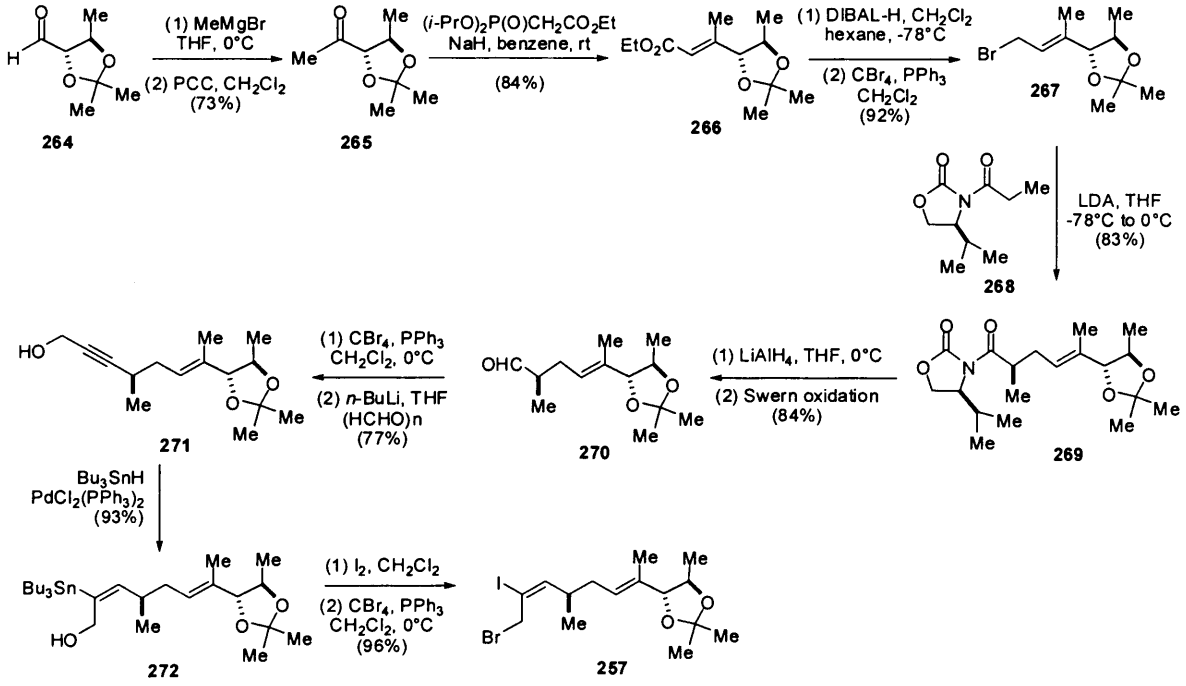
Scheme 60. Kibayashi's retrosynthetic analysis of allopumiliotoxins

The synthesis of pyrrolidine **256** commenced with the preparation of ketone **259** with a thiol esterification-Grignard reaction of *N*-Boc-L-proline **215** (Scheme 61). Deprotection of **259** with trifluoroacetic acid afforded the pyrrolidine trifluoroacetate salt, which was immediately treated with 3-lithio-1,3-dithiane to produce the tertiary alcohol **260** as a single diastereoisomer consistent with a Cram chelation-controlled transition state. The cyclic dithioacetal group of **260** was converted to the dimethyl acetal with methanol and $Hg(ClO_4)_2$. Protection the amino group with a cyanomethyl group afforded compound **261**. *O*-benzylation of the tertiary alcohol was then achieved using benzyl bromide and potassium hydride. Removal of the cyanomethyl group with $AgNO_3$ and subsequent *N*-protection by the Z group afforded carbamate **262**. Acetal hydrolysis and $NaBH_4$ reduction of the resulting aldehyde proceeded in very good yield to provide alcohol **263**. Silylation of alcohol **263** and hydrogenolytic removal of the Z group resulted in **256**. Pyrrolidine **256** was prepared in 13 steps and 14 % yield from *N*-Boc-L-proline.



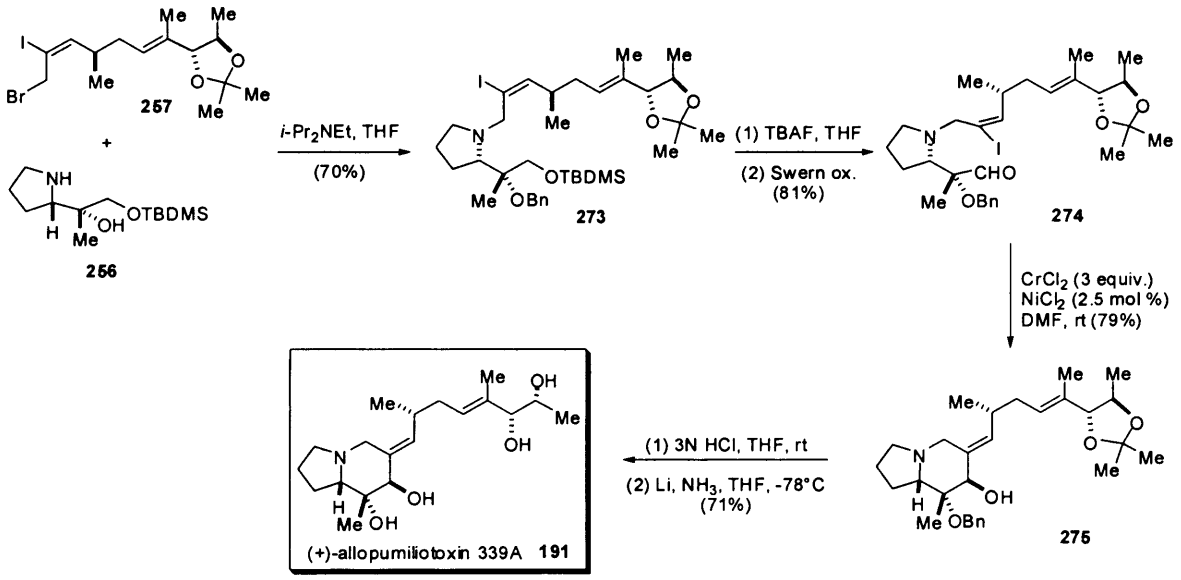
Scheme 61. Synthesis of **256**

The side chain segment was elaborated from the known D-4-deoxythreose derivative (Scheme 62). Aldehyde **264** was first subjected to Grignard reaction with MeMgBr followed by PCC oxidation to afford the methyl ketone **265** which was converted to the (*E*)-olefin **266** by Horner-Emmons condensation. The ester group was reduced to the alcohol that was transformed to the bromide **267** under standard conditions. Evans alkylation with propionyl oxazolidinone **268** was used to install the *R* stereogenic center of compound **269**. The Evans auxiliary was cleaved with $LiAlH_4$ and the resulting alcohol oxidised under Swern conditions to give aldehyde **270**. Treatment of aldehyde **270** with CBr_4 and PPh_3 provided a dibromide, which was converted to the propargylic alcohol **271** by reaction with butyllithium and paraformaldehyde. Synthesis of **271** was performed in 10 steps and 30% overall yield from aldehyde **264**. Palladium-catalysed hydrostannation of **266** furnished the (*E*)-2-(tributylstannyl)alkene **272** in 93% yield along with a minor amount (3.8%) of its regioisomer. Iododestannylation gave the (*E*)-iodoalkene, which was then transformed to the desired allylic bromide **257** in 96% yield.



Scheme 62. Preparation of allylic bromide **257**

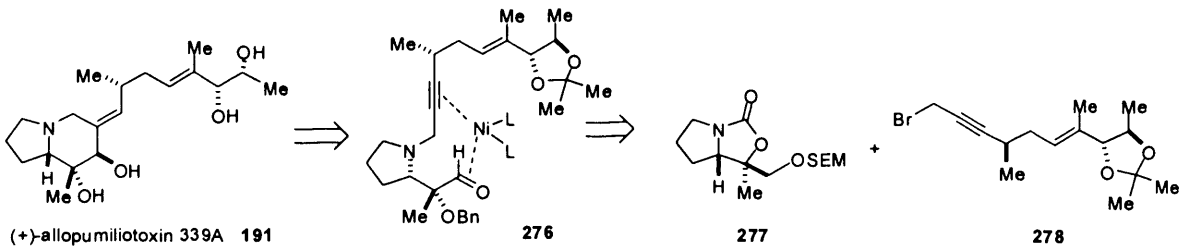
The final route that led to (+)-allopumiliotoxin 339A is shown in scheme 63. Coupling of bromide **257** and amine **256** in the presence of the Hunig's base provided compound **273** in 70% yield. Desilylation of **273** followed by Swern oxidation afforded aldehyde **274**. Cyclisation was performed smoothly in 79% yield by treatment with nickel(II)/chromium(II) and with complete stereoselectivity to afford compound **275**. Cleavage of the isopropylidene group followed by debenzylation gave (+)-allopumiliotoxin 339A **191** in 71% yield. This synthesis of (+)-allopumiliotoxin 339A was achieved in 19 steps and 4.5% yield from *N*-(*tert*-butoxycarbonyl)-L-proline and 24 steps and <4% yield from L-threonine.



Scheme 63. Preparation of (+)-allopumiliotoxin 339A by Kibayashi *et al.*

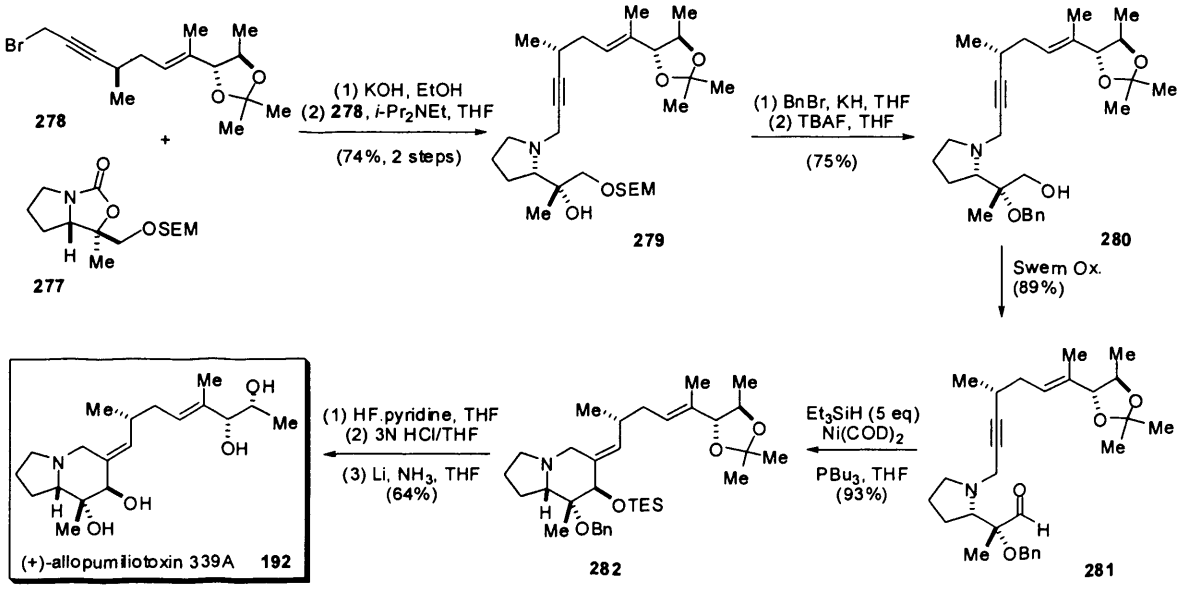
5.3.4.2. Nickel Catalysed Synthesis

In 1999, Montgomery and Tang reported a nickel catalyzed synthesis of (+)-allopumiliotoxin 339A as summarised in Scheme 64.[76] Their synthesis involved a triethylsilane-promoted cyclisation of ynal **276**.



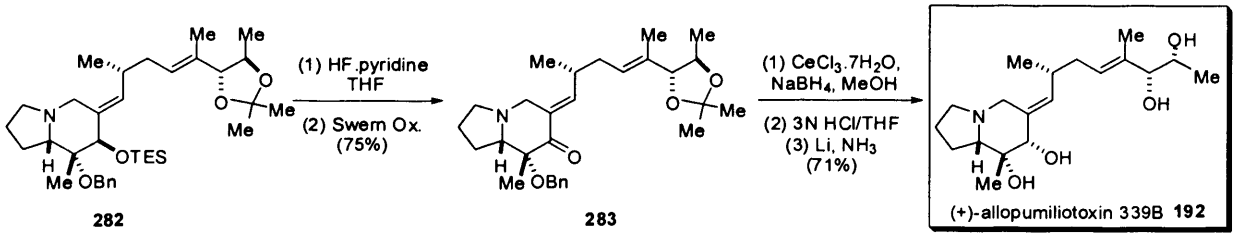
Scheme 64. Montgomery and Tang's retrosynthetic plan to (+)-allopumiliotoxin 339A

Synthesis of the alkylideneindolizidine ring began with the coupling of compound **277** with bromide **278** in the presence of Hunig's base in 92% yield (Scheme 65). Oxazolidinone **277** was prepared from L-proline methyl ester following Overman's procedure[71] as illustrated in Scheme 58 and propargyl bromide **278** by bromination of the corresponding alcohol **271** used in Kibayashi total synthesis of allopumiliotoxin 339A.[75] Benzylation of the tertiary alcohol and desilylation of the primary alcohol led to alcohol **280** in 75% yield. Alcohol **280** was then oxidised under Swern conditions to yield the cyclisation substrate **281**. Aldehyde **281** was then treated with triethylsilane (5 eq), $Ni(COD)_2$ (0.2 eq) and tributylphosphine (0.8 equ) in THF at 0°C for 18 h to afford bicycle **282** as a single diastereoisomer in 93% yield. After removal of all the protecting groups, (+)-allopumiliotoxin 339A **191** was obtained in 64% yield.



Scheme 65. Synthesis of (+)-allopumiliotoxin 339A by Montgomery *et al.*

It is noteworthy that this route also led to (+)-allopumiliotoxin 339B: after removal of the silyl group from compound **282**, the alcohol was oxidised under Swern conditions. The resulting ketone **283** was stereoselectively reduced with $CeCl_3/NaBH_4$ in methanol in 95% yield. Deprotection with 3N HCl and then Li/NH_3 afforded (+)-allopumiliotoxin 339B **192** (Scheme 66).

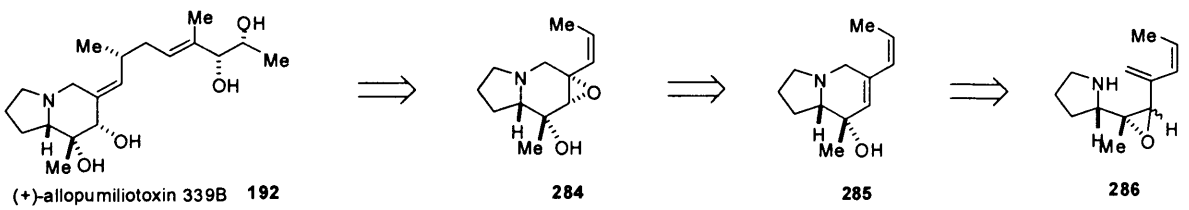


Scheme 66. Synthesis of (+)-allopumiliotoxin 339B by Montgomery *et al.*

5.4. Others Approaches to Pumiliotoxins and Allopumiliotoxins Indolizines Core

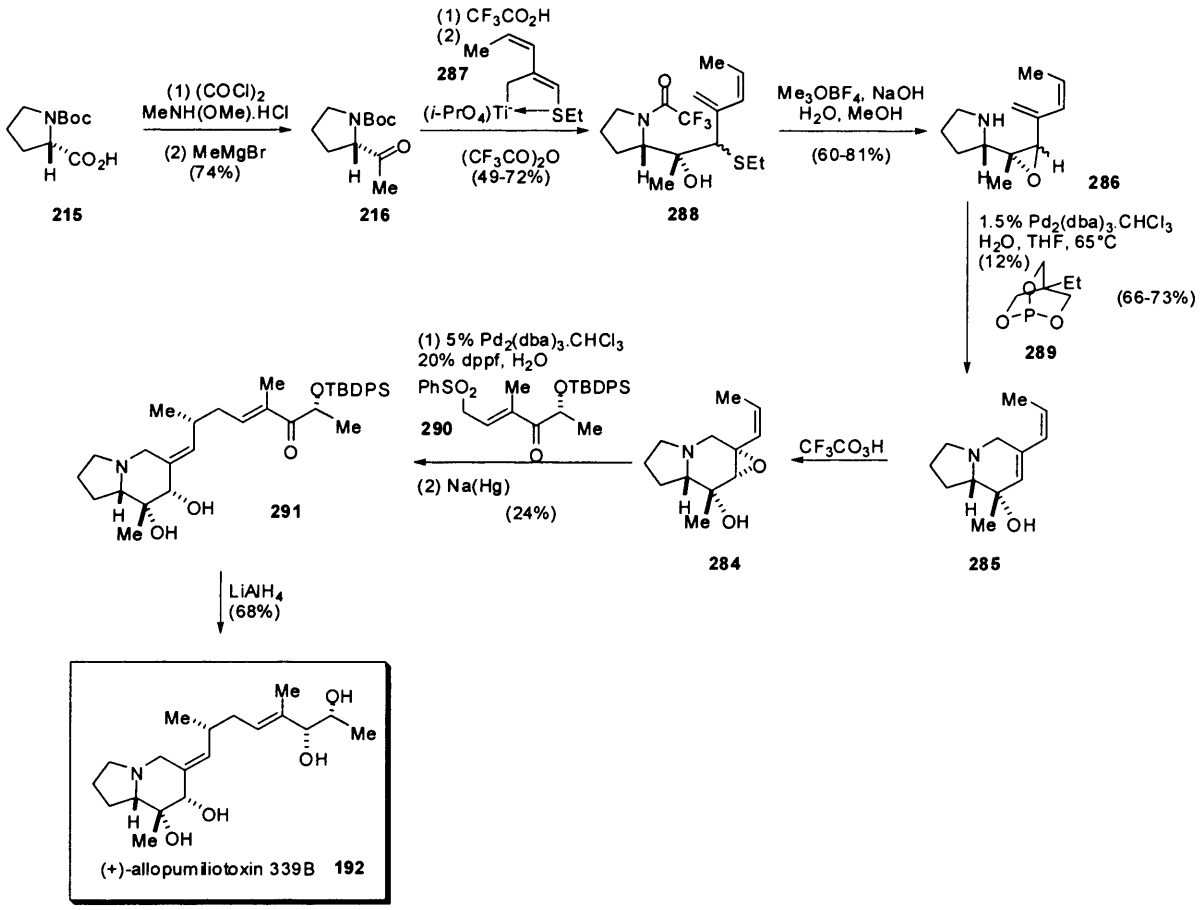
5.4.1. Trost's Total Synthesis of Allopumiliotoxin 339B

Trost and Scanlan reported a synthesis of allopumiliotoxin 339B using Pd(0) chemistry.[77] A Pd(0)-mediated allylic alkylation of epoxide **284** was used to transfer the chirality from the indolizine ring to the side chain and a Pd(0)-mediated cyclisation of vinyl epoxide **286** was employed to forge the piperidine ring (Scheme 67).



Scheme 67. Trost's retrosynthetic plan to (+)-allopumiliotoxin 339B

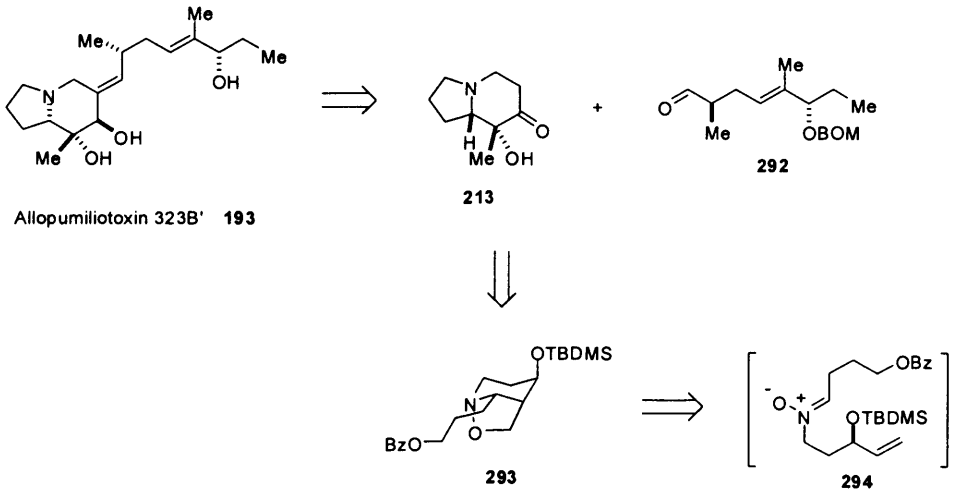
Once again, *N*-Boc-L-proline was the starting material of choice as shown in Scheme 68. Cyclisation precursor **286** was generated by chelation-controlled addition of allyltitanium intermediate **287** to the unprotected 2-acetylpyrrolidine generated from ketone **216**. S-Methylation and subsequent base treatment yielded epoxide **286**. The best result for the cyclisation step was obtained using $Pd_2(dba)_3.CHCl_3$ as the catalyst and compound **289** as the chiral ligand. Formation of epoxide **284** was achieved using CF_3CO_3H. Palladium(0)-catalysed condensation of vinyl epoxide **284** and allyl sulfone **290** proceeded with a perfect chirality transfer from C(6) to C(11) using $Pd_2(dba)_3.CHCl_3$ and dppf in the presence of water. Direct reductive desulfonylation of the crude product provided ketone **291** in 24% yield from epoxide **284**. Reduction-desilylation of compound **291** yielded (+)-allopumiliotoxin 339B **192**. The total synthesis was accomplished in 11 steps and <3% yield from *N*-(*tert*-butoxycarbonyl)-L-proline.



Scheme 68. Trost's total synthesis of (+)-allopumiliotoxin 339B

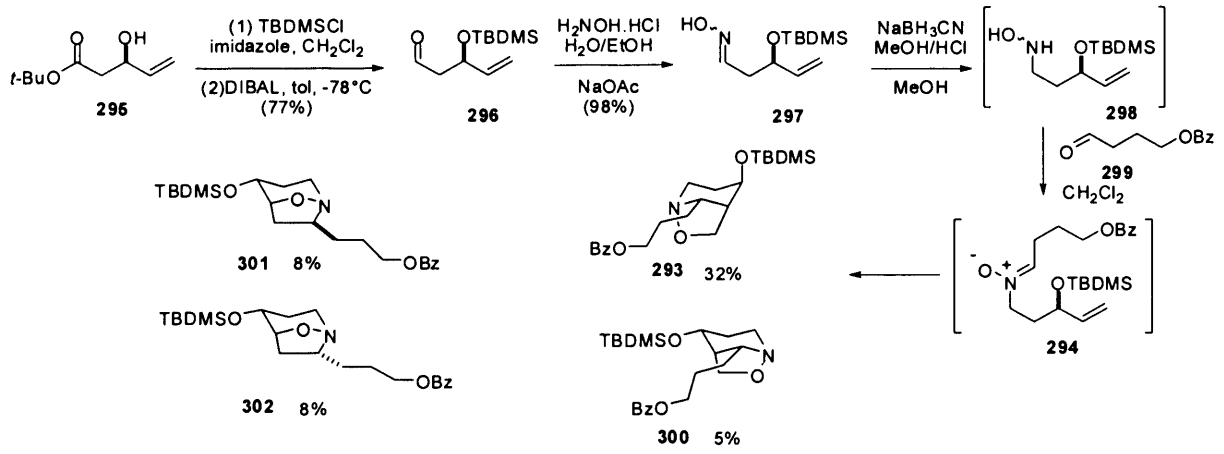
5.4.2. Holmes' Total Synthesis of Allopumiliotoxin 323B'

Holmes and Tan reported the first synthesis of an allopumiliotoxin alkaloid that did not use a proline derivative as a starting material.[78,79] Their strategy was based on an aldol condensation of aldehyde **292** with the potassium enolate of the indolizine core **213** (Scheme 69). The indolizine core **213** was synthesised from the isoxazolidine **293**, which can be derived from an intramolecular [3 + 2] cycloaddition reaction of the (*Z*)-*N*-alkenylnitrone **294**.



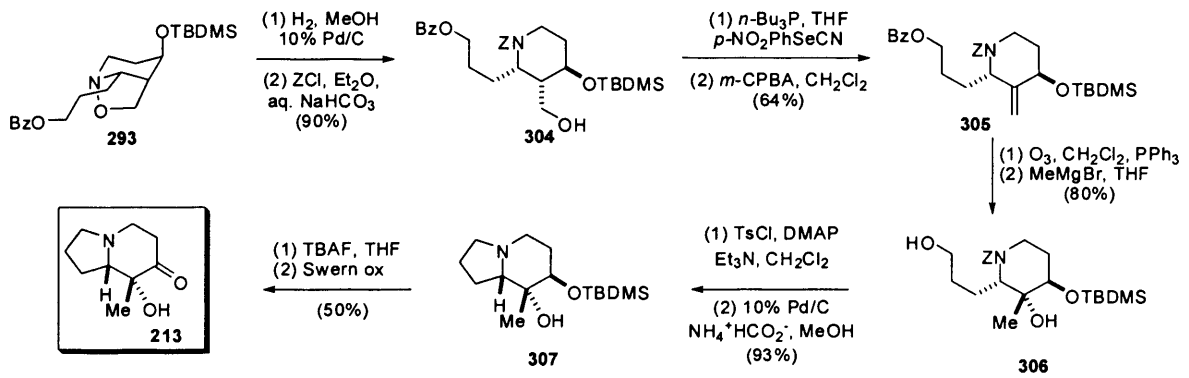
Scheme 69. Retrosynthetic analysis to (+)-allopumiliotoxin 323B' by Holmes *et al.*

The synthesis began with (*R*)-*tert*-butyl-3-hydroxy-pent-4-enoate **295** which was obtained by enzymatic resolution with Amino PS lipase (Scheme 70). After silylation of the alcohol, the ester group was reduced with DIBAL-H into the aldehyde **296**. Treatment with hydroxylamine gave oxime **297** which was subsequently subjected to a 2 steps reduction-condensation procedure to provide the (*Z*)-*N*-alkenylnitrone **294**. The intramolecular [3 + 2] cycloaddition reaction was carried out by heating a dilute solution of the crude nitrone **294** in toluene for 18 h at 70°C to give four oxazolidine cycloadducts. Isoxazolidine **293** was obtained in 32% yield and was separated by flash chromatography.



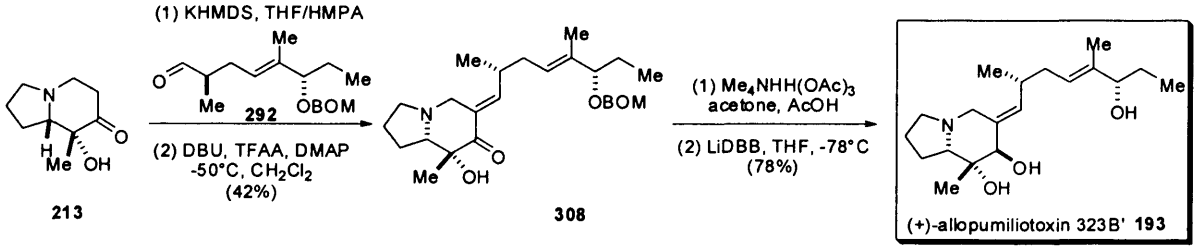
Scheme 70. Synthesis of oxazolidine **293**

Hydrogenolysis of isoxazolidine **293** followed by Z protection of the resulting free amino group provided the hydoxymethyl Z-protected piperidine **304** in 90% yield (Scheme 71). The dehydration the primary alcohol to form exocyclic alkene **305** was achieved by formation of a selenide followed by oxidation with one equivalent of *m*-chloroperoxybenzoic acid. Ozonolysis of alkene **305** gave a ketone that was subjected to a diastereofacial selective nucleophilic addition with an excess MeMgBr. Concomitant removal of the benzoyl group occured at this stage of the synthesis and provided alcohol **306**. Selective tosylation of the primary alcohol and removal of the benzyloxycarbonyl group triggered an intramolecular ring closure that yielded the indolizidine **307**. Desilylation and Swern oxidation gave the desired indolizidone core **213** in 50% yield.



Scheme 71. Holmes's route to Overman intermediate **213**

The synthesis of the side chain aldehyde **292** was achieved in 8 steps and 30% overall yield.[79] The aldol condensation between aldehyde **292** and the indolizidone core **213** was carried out using KHMDS and a mixed solvent (HMPA/THF)(Scheme 72). Direct dehydration afforded **308** in 42% yield. Reduction using tetramethylammonium triacetoxyborohydride and a catalytic amount of acetic acid in acetone gave the *anti*-diol as the only observable product. Finally, removal of the BOM protecting group using lithium di-*tert*-butylbiphenyl provided (+)-allopumiliotoxin 323B' **193**. This synthesis was achieved in 20 steps and 1.7% overall yield from the *β*-hydroxyester **295** and was significantly different from other previous syntheses by contructing the chiral azabicyclic core in avoidance of using L-proline or its derivative.

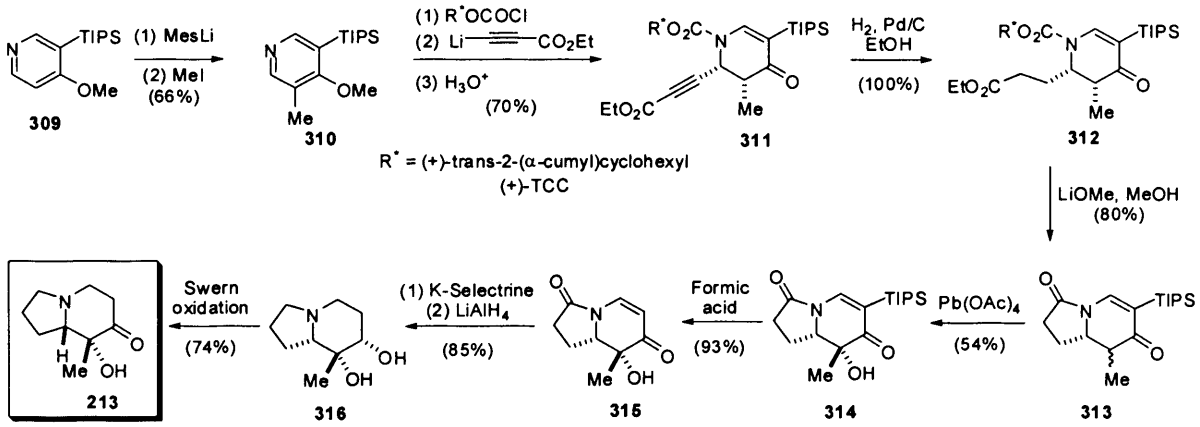


Scheme 72. Total synthesis of (+)-allopumiliotoxin 323B' by Holmes *et al.*

5.4.3. Comins' Total Synthesis of Allopumilotoxin 267A

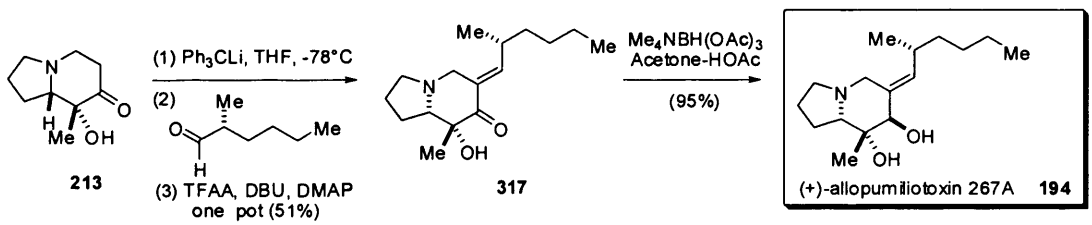
More recently, Comins and co-workers devised a route to (+)-allopumiliotoxin 267A using an enantiopure dihydropyridone building block.[80] Once again, an aldol condensation strategy was chosen and the synthesis of Overman's intermediate **213** was the key issue of the synthesis (Scheme 73). The synthesis commenced by lithiation of pyridine **309** with mesityl lithium[81] followed by treatment with methyl iodide to give pyridine **310**. To a 1-acylpyridium salt, prepared *in situ* from pyridine **310**, and (+)-TCC chloroformate, was added lithiated ethyl propiolate. An acidic work-up provided dihydropyridone **311** in 70% yield and 96% de. Catalytic hydrogenation of the triple bond afforded compound **312** and did not affect the enone system protected with the TIPS group. Removal of the chiral auxiliary with lithium methoxide resulted in cyclisation and provided indolizidinone **313** as an 8:1 mixture of diastereoisomers. This mixture

was subjected to an acetoxylation in a stereocontrolled manner using lead acetate in refluxing AcOH/*m*-hexafluoroxylene to give compound **314**. Protodesilylation of **314** using formic acid afforded compound **315**, which was reduced using K-Selectride followed by lithium aluminium hydride to afford diol **316** in 83% yield. Finally, oxidation under Swern conditions provided Overman's intermediate **213**.



Scheme 73. Comins' route to Overman intermediate **213**

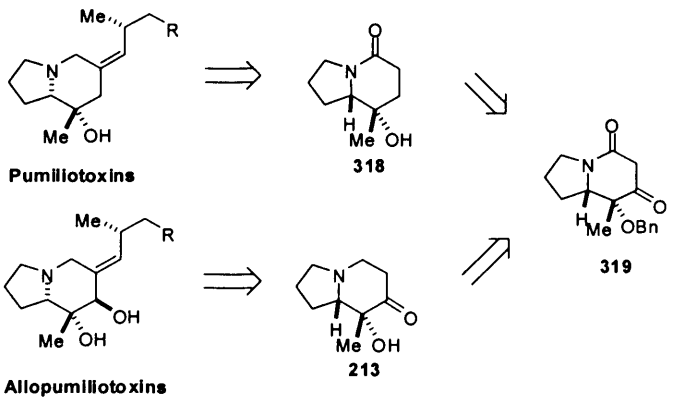
Overman's intermediate **213** was converted to (+)-allopumiliotoxin 267A in 48% yield using a modified literature procedure (Scheme 74).[64]



Scheme 74. Final steps to (+)-allopumiliotoxin 267A **194**

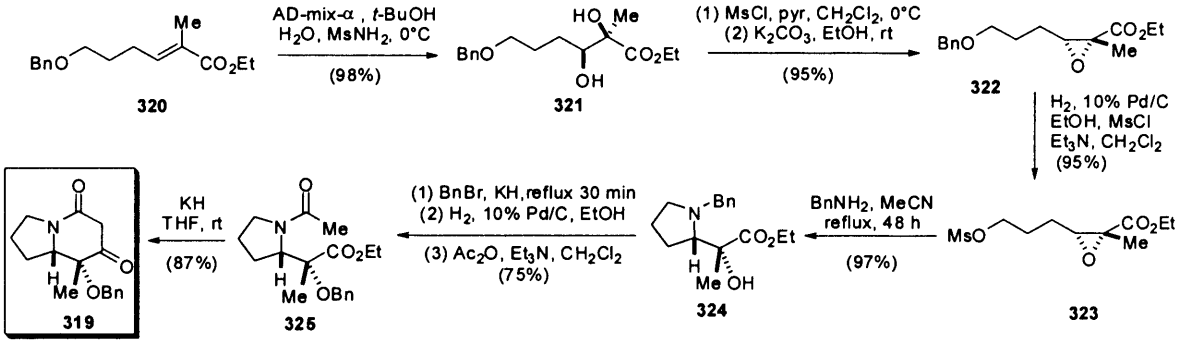
5.4.4. Lin's Approach to the Indolizidine Core of Pumiliotoxins and Allopumiliotoxins

In 2003, Lin and co-workers developed a method to construct the chiral azabicyclic core without using proline and its homologue.[82] As shown in retrosynthetic analysis depicted in Scheme 75, a common key intermediate was used to access both pumiliotoxins and allopumiliotoxins. Their strategy was based on an intramolecular aminolysis of epoxide.



Scheme 75. Lin's retrosynthetic analysis of pumiliotoxin alkaloids from **319**

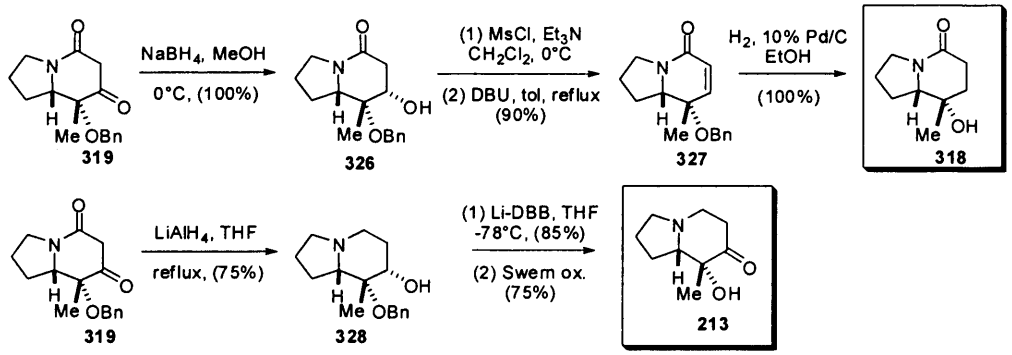
The synthesis started from a Sharpless asymmetric dihydroxylation of the trisubstituted olefin **320** that afforded diol **321** in 98% yield and 95% ee (Scheme 76). A monomesylation of the secondary alcohol followed by treatment with K_2CO_3 yielded epoxide **322**. After hydrogenolytic cleavage of the benzyl group, the alcohol was activated into mesylate **323**. A stepwise substitution-ring-opening sequence took place gently after treatment of benzylamine in refluxing MeCN to provide the pyrrolidine derivative **324** as a single isomer. Protection of the tertiary alcohol, followed by selective removal of *N*-benzyl and acetylation afforded acetamide **325** in 75% yield. A Claisen condensation was then successfully achieved using potassium hydride and gave the desired intermediate **319**.



Scheme 76. Preparation of intermediate **319**

Sodium borohydride reduction of ketone **319** furnished alcohol **326** that was converted to its mesylate and subjected to elimination under basic conditions to provide compound **327** in 90% yield (Scheme 77). The pumiliotoxin intermediate **318** was obtained after saturation of the double bond and debenzylation in quantitative yield.

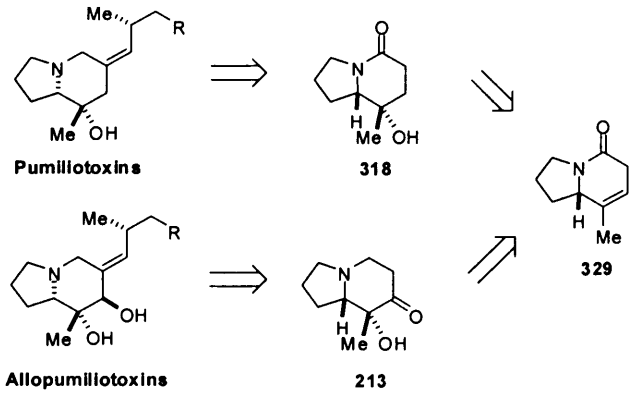
The allopumiliotoxin intermediate **213** was obtained after reduction with $LiAlH_4$ of lactam **319**, followed by benzyl deprotection and Swern oxidation.



Scheme 77. Preparation of the indolizidine core of pumiliotoxins and allopumiliotoxins from **319**

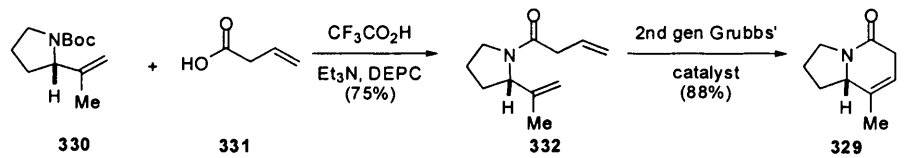
5.4.5. Stevenson's Rapid Synthesis of the Indolizidine Core of Pumiliotoxins and Allopumiliotoxins

More recently, Stevenson *et al.* reported a rapid synthesis of the two key intermediates **318** and **213** in the synthesis of pumiliotoxins and allopumiliotoxins.[83] Their retrosynthesis analysis is summarised in Scheme 78.



Scheme 78. Stevenson's retrosynthetic analysis of pumiliotoxin alkaloids from alkene **329**

These 2 key indolizidines were prepared from a common alkene precursor **329** whose synthesis is depicted in Scheme 79. The synthesis commenced from the known carbamate[61] **330** that was deprotected and coupled *in situ* with 3-butenoic acid **331** to afford alkene **332**. A ring closing metathesis using second generation Grubbs' catalyst provided alkene **329** in 88% yield.

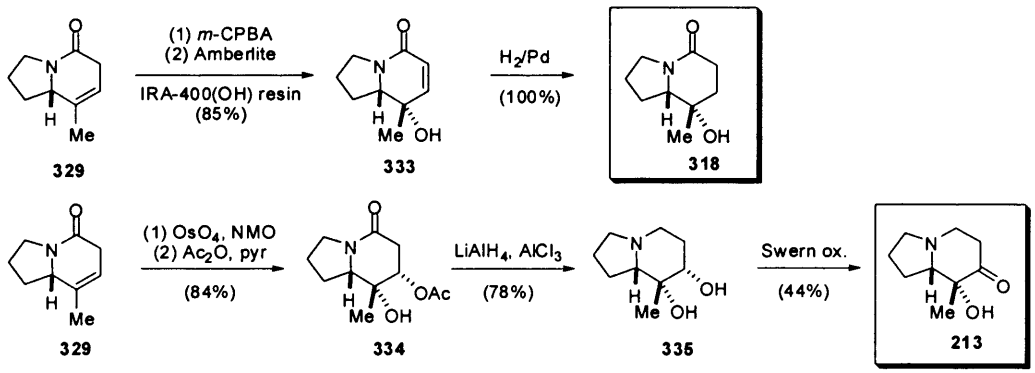


Scheme 79. Preparation of key intermediate **329**

The synthesis of the pumiliotoxin intermediate **318** started with epoxidation of alkene **329** with *m*-CPBA. An *in situ* ring opening reaction using strongly basic ion-exchange resin Amberlite

IRA-400-(OH) afforded alkene **333** in 85% yield. Hydrogenation over a palladium catalyst provided the desired intermediate **318**.

To obtain the allopumiliotoxin intermediate **213**, osmium tetroxide catalysed dihydroxylation was achieved on alkene **329**. An acetylation was performed to isolate the polar water-soluble product **334**. After reduction of amide **334** and Swern oxidation of alcohol **335**, the key allopumiliotoxin intermediate was isolated in 34% yield from alkene **329**. An X-ray structure of diol **335** confirmed the stereochemistry of the intermediate.



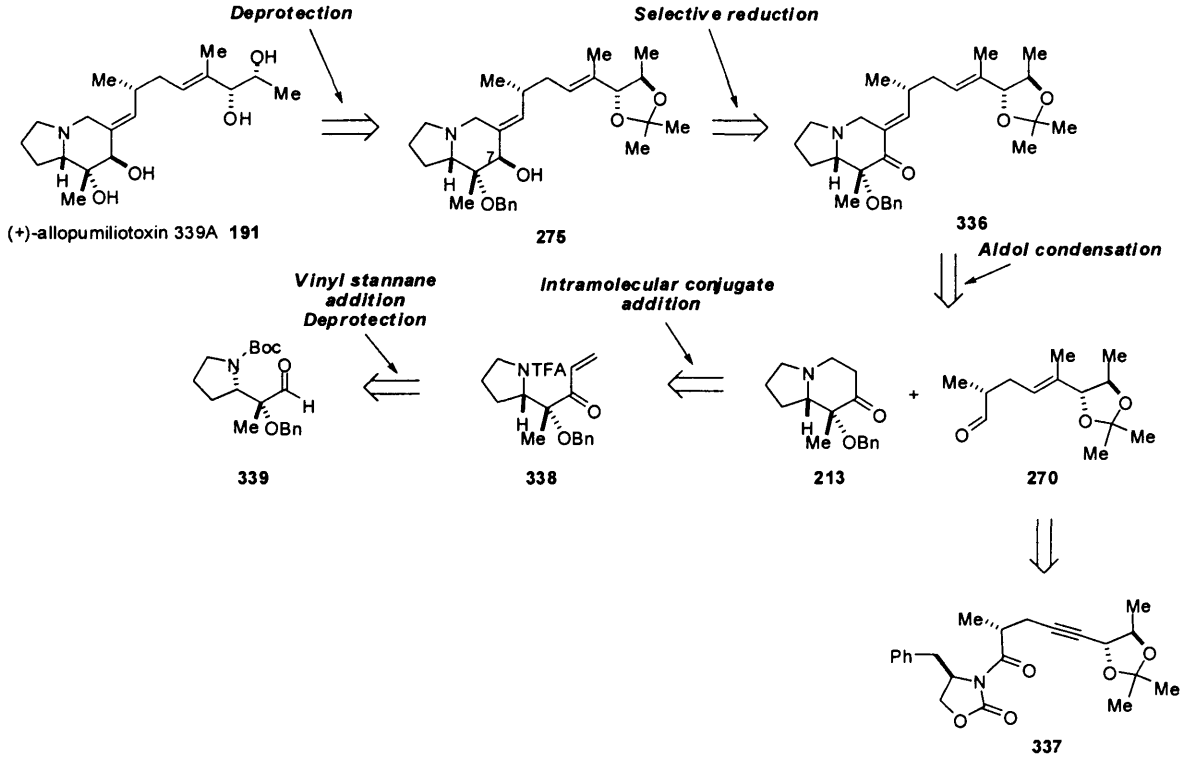
Scheme 80. Synthesis of Overman's intermediate by Stevenson *et al.*

6. Synthetic efforts towards (+)-Allopumiliotoxin 339A

6.1. Retrosynthetic Analysis of (+)-Allopumiliotoxin 339A

There were two main aims guiding our retrosynthetic planning for (+)-allopumiliotoxin 339A. First, we wished to demonstrate the utility of the recently developed *O*-directed free radical hydrostannation of disubstituted acetylenes with Ph_3SnH/Et_3B/air in total synthesis. Secondly, we wished to develop a very flexible route capable of being readily modified to create novel analogues for future biological testing.

(+)-Allopumiliotoxin 339A would be synthesised from its protected form **275** as shows in Scheme 81. The last steps of the synthesis would involve acidic deprotection of the isopropylidene, and *O*-debenzylation with Li/ammonia as previously described.[74] Indolizidine **275** would be prepared from ketone **336** *via* a hydroxyl directed reduction using $Me_4NBH(OAc)_3$ analogously to that used in the synthesis of (+)-allopumiliotoxin 267A (Scheme 74).[64] Enone **336** would be constructed by an aldol condensation of ketone **213** with aldehyde **270** followed by dehydration; the geometry would arise from the desire to minimise steric repulsions in the product. Although, this aldol methodology has been widely used in the total synthesis of various pumiliotoxins and allopumiliotoxins, it has never been applied in the synthesis of (+)-allopumiliotoxin 339A. Intermediate **213** appeared derivable from enone **338** by a base-inducted intramolecular conjugate addition. Enone **338** would itself be prepared from a vinyl stannane addition to α-alkoxyaldehyde **339** followed by oxidation of the resulting alcohol and deprotection of the Boc-group. Aldehyde **270** would be made by removal of the auxiliary from intermediate **337** followed by reduction.

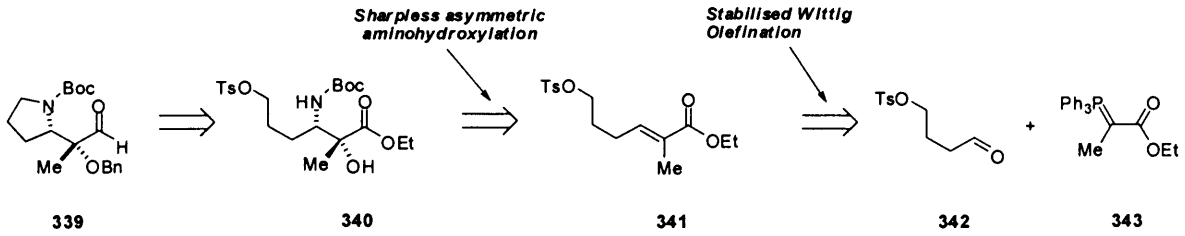


Scheme 81. Retrosynthetic plan for (+)-Allopumiliotoxin 339A **191**

6.2. Synthetic Studies Towards α-Alkoxyaldehyde 339

6.2.1. First Generation Strategy for α-Alkoxyaldehyde 339

6.2.1.1. Retrosynthetic analysis



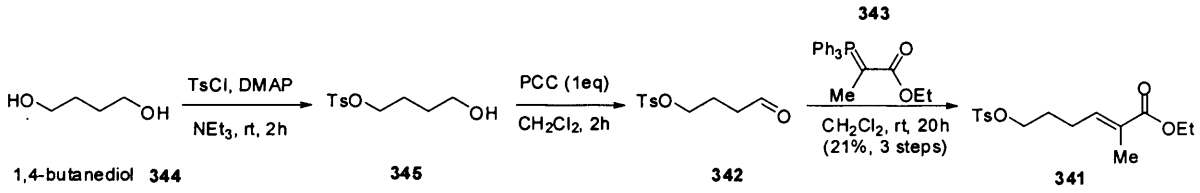
Scheme 82. Initial retrosynthetic plan for α-alkoxyaldehyde **339**

Our approach to α-alkoxyaldehyde **339** would avoid the use of L-proline as a starting material, to allow for flexibility in ring substitution patterns and different ring sizes in analogues. α-Alkoxyaldehyde **339** appeared derivable from compound **340** *via* intramolecular S_N2 cyclisation. According to Baldwin's Rules, a 5-*exo-tet* ring closure of this sort should be favourable. Reduction of the ester to the aldehyde would complete the synthesis. The key step to introduce the 2,3-*syn*-aminoalcohol motif would be a regioselective Sharpless asymmetric aminohydroxylation (SAA) performed on alkene **341**. The trisubstituted alkene would be prepared by a Wittig condensation between aldehyde **242** and the Marshall phosphorane **343**, an ylide well known to favour this stereochemical outcome.

6.2.1.2. Attempted Implementation of the Sharpless Asymmetric Aminohydroxylation Strategy for α-Alkoxyaldehyde **339**

The synthesis of a suitable precursor for the Sharpless asymmetric aminohydroxylation was first investigated; we explored a variety of procedures to form the monoprotected alcohol **345** from 1,4-butanediol **344**. The use of silver oxide and potassium iodide described by Bouzide and Sauve was too expensive to be applied for the first step of our total synthesis.[84] Choudary *et al.* have reported a monotosylation of 1,4-butanediol mediated by metal-exchanged

Montmorillonite clay catalyst.[85] The preparation of the catalyst was not straightforward and thus we decided to use Ahlberg and Wu's method.[86] The tosylation was achieved in absence of solvent employing *p*-toluenesulfonyl chloride as tosylating agent in presence of DMAP (0.04 eq) and triethylamine (1.05 eq) in 1,4-butanediol (7.7 eq). The original authors found that the use of solvent favoured the formation of the ditosylate and recommended that the extractive work-up with dichloromethane be conducted as quickly as possible. Two spots appeared on TLC with anisaldehyde, the more polar one was the mono-protected alcohol **345** and the faster moving the diprotected alcohol. The product **345** could not be stored as it decomposed into the diprotected alcohol. Furthermore, the mono-protected alcohol **345** could not be isolated as it decomposed into the diprotected alcohol during purification by SiO_2 flash chromatography. As a consequence, the PCC oxidation was performed on the crude mixture in dichloromethane at room temperature. After a quick purification on a pad of silica gel, the unstable aldehyde **342** was reacted with carbethoxyethylidene triphenylphosphorane **343** in dichloromethane at room temperature overnight. In this Wittig olefination, the use of phosphorane **343** gave rise to the *E*-alkene selectively. Evaporation and purification by SiO_2 chromatography led to alkene **341** in 21% yield over 3 steps (Scheme 83).

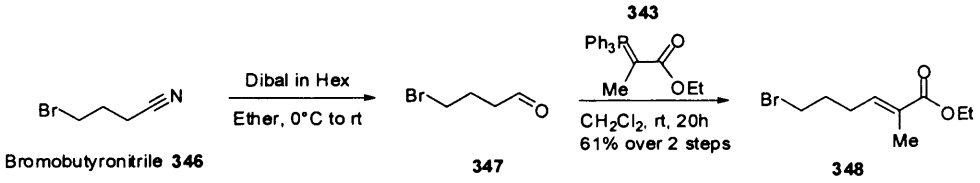


Scheme 83. Synthesis of alkene **341**

Evidence for the formation of this alkene was given by the presence of a tq at δ 6.54 ppm on the 500 MHz spectrum of **341** in $CDCl_3$. The chemical shift of an alkene proton is influenced by other alkene substituents and can be predicted using the formula δ = 5.2 + Zgem + Zcis + Ztrans.[87] In our case, we should have δ 6.6 ppm for the *E*-alkene and δ 6.3 ppm for the *Z*-alkene. Our chemical shift of δ 6.54 ppm is in favour of the *E*-isomer.

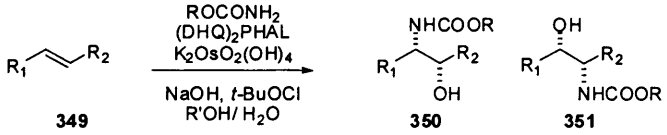
The low yield obtained for the synthesis of alkene **341** led us to develop a new intermediate for the Sharpless asymmetric aminohydroxylation. It was thought that the *p*-toluenesulfonyl leaving group might be beneficially replaced by a bromide, and the synthesis

of bromide **348** was therefore investigated. The developed route, depicted in Scheme 84, commenced with the reduction of bromobutyronitrile **346** with DIBAL-H in ether at 0°C.[88] This furnished aldehyde **347** after hydrolysis of the intermediary imine. Aldehyde **347** was volatile, and so the crude product was reacted directly with carboethoxyethylidene triphenylphosphorane **343** to afford olefin **348** as a yellow oil in 61% yield over 2 steps. Analysis by 500 MHz ^{1}H NMR confirmed the formation of the *E*-alkene with the presence of a tq at 6.68 ppm. Again, the olefinic proton is deshielded because of the presence of the *cis*-carbonyl, the geometry is thus confirmed.



Scheme 84. Synthesis of alkene **348**

With precursors **341** and **348** in hand, we investigated the Sharpless asymmetric aminohydroxylation, which provides protected vicinal aminoalcohols enantioselectively in a single step from alkenes as illustrated in Scheme 85.



Scheme 85. The Sharpless Asymmetric Aminohydroxylation

The SAA was first reported in 1996 as a process in which the nitrogen source was the chloramine salt of a sulphonamide **352**.[89] Since then, various alternative nitrogen sources have been investigated and the sulfonamides can be replaced by alkyl carbamates **353** or by amides **354** (Figure 16). Therefore, a large number of aminoalcohol products can be obtained depending on which protecting group is desired. In each case, the reactive species is the alkali metal salt made *in situ* from the *N*-halogenated compound derived from the sulfonamides, carbamates and amides.

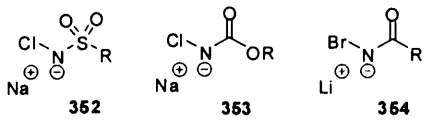


Figure 16. The nitrogen sources used in the SAA

The enantioselectivity of the reaction results from the presence of chiral ligands that favour addition to one enantiopic face of the alkene. The asymmetric induction follows the rules described for the Sharpless Asymmetric Dihydroxylation (AD);[29] $(DHQD)_2PHAL$ directs addition to the β-face and $(DHQ)_2PHAL$ to the α-face (Figure 17).

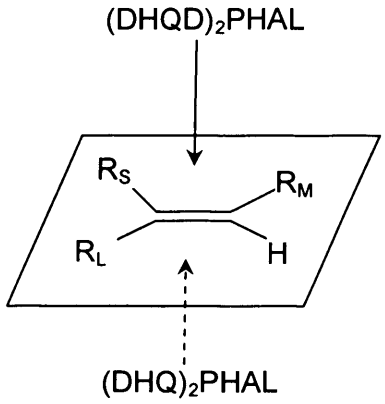
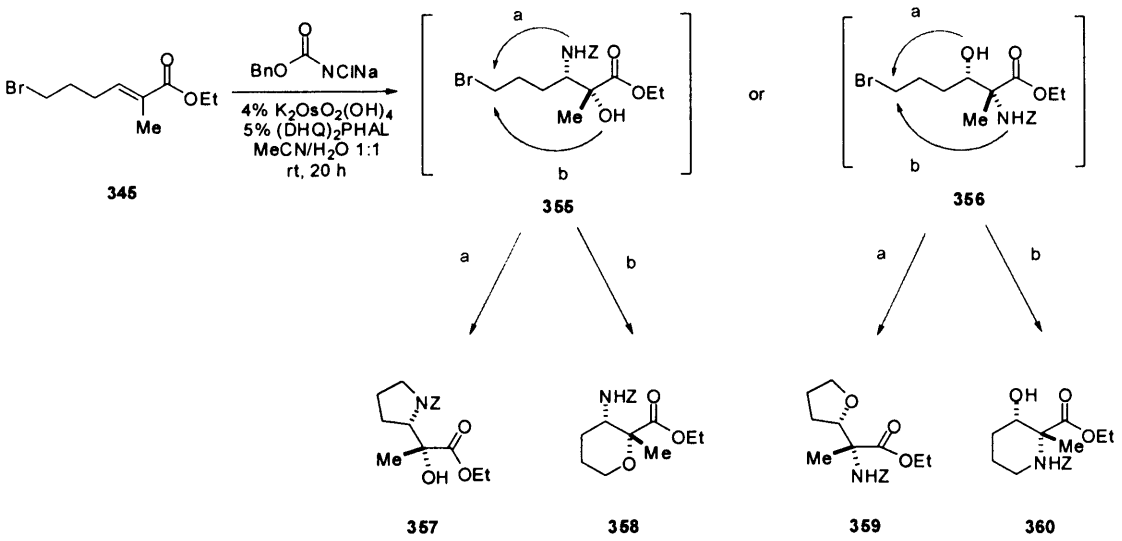


Figure 17. The Sharpless model for the asymmetric hydroxylation

One of the new challenges of the SAA is the control of the regioselectivity which can be influenced by many factors. However, it has been found that, generally, the nitrogen prefers to add on the less substituted end of the alkene. In the case of a trisubstituted alkene, the steric hindrance at one end is so high compared to the other that the SAA usually only gives the less hindered amine product. Finally, $K_2OsO_2(OH)_4$ is generally used as a catalyst.

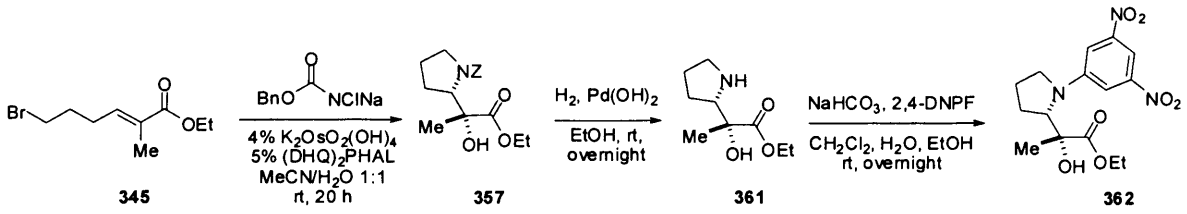
Returning to our particular case, $(DHQ)_2PHAL$ would give rise to the desired enantioselectivity according to the AD mnemonic proposed by Sharpless depicted in Figure 17.

A carbamate-based nitrogen source[90] was the more attractive nitrogen source in our system **341** or **348** as it would allow to fix directly the Boc group onto the nitrogen. The sodium salt of the *N*-chlorocarbamate was made *in situ* from *tert*-butylcarbamate, *tert*-butylhypochlorite,[91] and aqueous NaOH following Sharpless' procedure.[92] A qualititative investigation of the solvent revealed that a mixture of acetonitrile/water was the solvent of choice leading to a partial consumption of the starting material. No reaction occurred with alkenes **341** and **348** according to TLC analysis when *n*-PrOH/water 2:1 was used, and the use of *n*-PrOH/water 1:1 led to degradation products. Difficulties were also encountered in removing unreacted *tert*-butylcarbamate and we did not manage to isolate any of the products that were formed. Nevertheless, we could see on TLC with anisaldehyde that at least 5 products had formed. Therefore, we decided to use benzylcarbamate as the nitrogen source in 1:1 MeCN/H_2O in the hope that its separation from the desired compound might be easier. Again five new spots appeared on the TLC along with the starting material that was not consumed completely. An extractive work-up with sodium sulfite and EtOAc afforded a complex mixture of products which was purified using SiO_2 flash chromatography. Unfortunately, it was not possible to completely purify the main product from the excess benzylcarbamate. TLC analysis showed that the aminohydroxylation of alkenes **341** and **348** led to the same main compound, hinting that a cyclisation might have occurred *in situ*. In fact, four different compounds can arise from the Sharpless Asymmetric Aminohydroxylation step depending on the regioselectivity of both the aminohydroxylation and the ring closure. The formation of these four compounds is shown in Scheme 86.



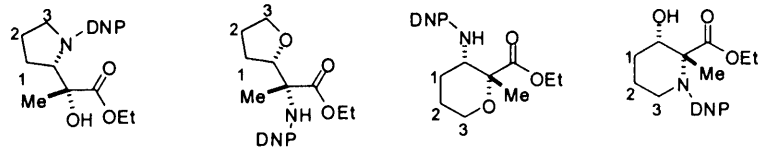
Scheme 86. Formation of the four possible products after the SAA

To establish the structure of the major product, hoped to be **357**, the Z group was hydrogenated with $Pd(OH)_2$ in ethanol and the resulting free amine was protected with a dinitrophenyl group as shown in Scheme 87.



Scheme 87. Formation of the DNP-derivative **362**

The four different compounds that could be obtained after the 2 step sequence described in Scheme 87 are depicted in Figure 18.



362 363 364 365

Figure 18.

The peaks of the proton and carbon spectra of the 2,4-dinitrophenylated product were first assigned using 500 MHz ^{1}H NMR, ^{13}C NMR, COSY, HMQC and DEPT experiments in $CDCl_3$. In fact, the CH close to the nitrogen was found much deshielded at δ 4.60 ppm. The use of COSY and HMQC experiments allowed attribution of the different CH_2 peaks. The protons on C3 are obviously the more deshielded at δ 3.58 and 2.73 ppm. Furthermore, a ^{1}H-^{1}H coupling was visible on the 500 MHz cosy spectrum between the protons on C3 and the one on C2. The protons of C2 were thus detected at δ 2.05 and 1.71 ppm and the one on C1 at δ 2.20 ppm.

Finally, analysis of the HMBC spectrum demonstrated that the cyclisation had given rise to a nitrogen-containing 5-membered ring (Figure 19). In the HMBC spectrum, a long-range ^{1}H-^{13}C coupling between the protons on C3 and the quaternary carbon of the DNP at δ 147.4 ppm was observed; hence compounds **363** and **364** could be ruled out. Additionally, there was a ^{1}H-^{13}C coupling between the hydrogen of the only CH of the ring with C3 at δ 62.3 ppm. A reciprocal ^{1}H-^{13}C coupling between the protons on C3 and the carbon of CH at δ 68.1 ppm was also observed. Thus structure **365** could be discarded. NMR studies confirmed the desired structure of **362** and as a consequence, the structure of compound **357**.

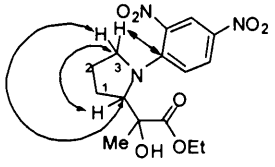
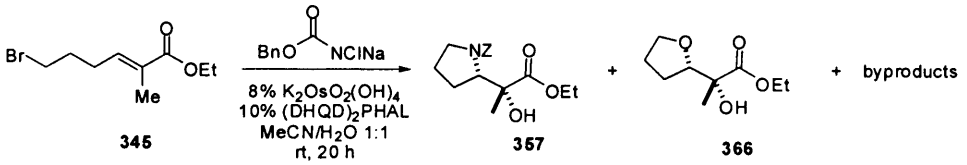


Figure 19. The long-range ^{1}H-^{13}C coupling in **362**

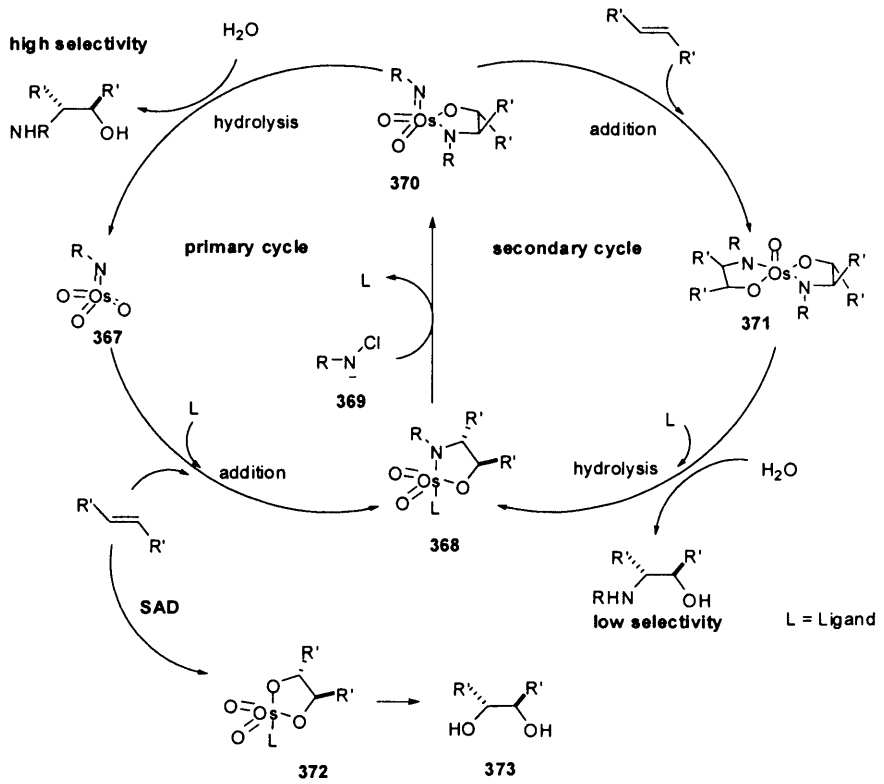
We were thus pleased to find that the formation of **357** occurred in one step. We now had to optimize the reaction using bromide **345** in order to increase the yield and solve the purification issues. The amount of catalyst $K_2OsO_2(OH)_4$ was increased from 5 to 8 mol% and the amount of ligand $(DHQ)_2PHAL$ from 6 to 10%. We were pleased to observe complete disappearance of the starting material according to TLC analysis. Again, a complex mixture of compounds was obtained and it was not possible to isolate all of them. Unfortunately, after purification on silica gel, the main blue spot visible on the TLC with anisaldehyde was found to be the tetrahydrofuran **366** arising from the cyclisation of the dihydroxylated product (Scheme 88).



Scheme 88. The Sharpless Asymmetric Aminohydroxylation of alkene **366**

Tetrahydrofuran **366** was contaminated with the excess benzylcarbamate and extensive purification by SiO_2 flash chromatography allowed isolation of a small amount of nearly pure tetrahydrofuran **366** in order to carry out analyses. Its structure was confirmed by its FAB HRMS which contained an $(M+H)^+$ peak at m/e 189.11286 (Calcd $(M+H)^+$ 189.11268 for $C_9H_{17}O_4$). Significantly, we increased the amounts of $K_2OsO_2(OH)_4$ and ligand in order to drive the reaction to completion, we instead favoured the formation of the dihydroxylated product which cyclised into tetrahydrofuran **366**.

The formation of the diol by-products during SAA reactions is a common issue. The main recommendations to avoid its formation are to decrease both the amount of water and of the osmium catalyst in the reaction mixture. The proportion of water was thus reduced to a 3:2 MeCN/water ratio. We could not reduce the proportion of water any further as the starting material remained untouched when a 2:1 MeCN/water mixture was used. To understand the role of water in the SAA, it is instructive to examine the proposed mechanism for the aminohydroxylation (Scheme 89).

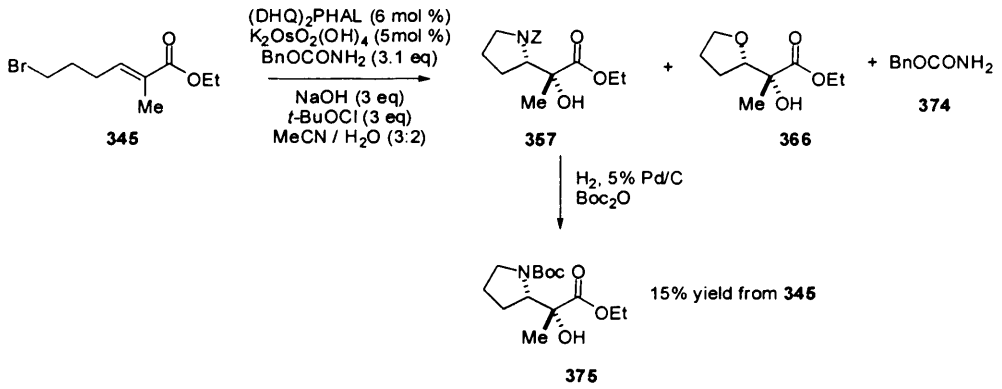


Scheme 89. A proposed mechanism for the SAA

This mechanism involves two catalytic cycles, each giving different selectivity pattern. In the primary cycle the alkene addition to the imidotrioosmium (VIII) species **367** is mediated by the ligand to give the osmium azaglycolate **368**. Species **370** is then formed after re-oxidation of **368** by the nitrogen source **369**. Azaglycolate **370** can then either be hydrolysed by water to afford the product with high selectivity or be attacked by the alkene and enter the secondary cycle. The limiting step in each cycle is the hydrolysis of the azaglycolate complexes by water. High water concentration is thus needed for the reaction to occur.[93] Moreover, if the concentration of the osmium catalyst is too high, the alkene can react directly with the catalyst and undergo a ligand-mediated asymmetric dihydroxylation reaction, to form an osmium (VI) glycolate complex **372**, analogous to the azaglycolate complex **368**. Formation of the diol **373** will ensue.

After much effort at optimizing the process, bromide **345** was used as the substrate and only 5% mol of the osmium catalyst was used. Furthermore, $K_2OsO_2(OH)_4$ was added at 0 °C, by small portions over 20 min. A quick purification by SiO_2 flash chromatography was achieved

to remove most by-products, and hydrogenation of the partially purified mixture in presence of Boc-anhydride[94] led to α-alkoxyester **375**. Decomposition of the excess benzylcarbamate **374** occurred under these reductive conditions and α-alkoxyester **375** could be purified successfully after SiO_2 flash chromatography and was obtained as a white foam in 15% yield from olefin **345** (Scheme 90).



Scheme 90. Improved conditions for the Sharpless Asymmetric Aminohydroxylation of **345**

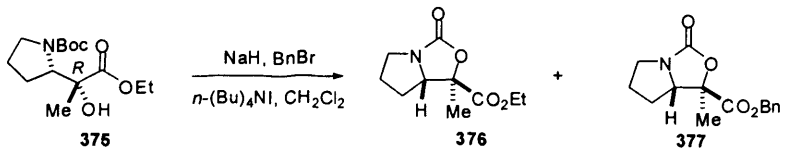
We finally developed a reproducible procedure for the synthesis of the α-alkoxyester **375**. Even though the yield was quite low, this method did allow us to install 2 stereocenters, to carry out the cyclisation and to protect the nitrogen in just 2 steps. The difficulties we met are probably due to the fact that the substrate is a trisubstituted alkene. In fact, there are very few examples in the literature in which trisubstituted alkenes have been used as substrates for the SAA. Barboni *et al.* could not apply the SAA in their synthesis of Paclitaxel, and used a SAD instead.[95] Clark *et al.* succeeded in 2001 using Chloramine-T as the nitrogen source.[96] Wang *et al.* did not try to use the aminohydroxylation in their work towards the Pumiliotoxin synthesis and prepared α-alkoxyester **324** from alkene **320** in five steps (Scheme 76).[82]

We next investigated the protection of alcohol **375**. Most of the conditions we tried left the alcohol untouched (Table 1, entry 2,4,5,6).

Table 1. Protection of alcohol **304**

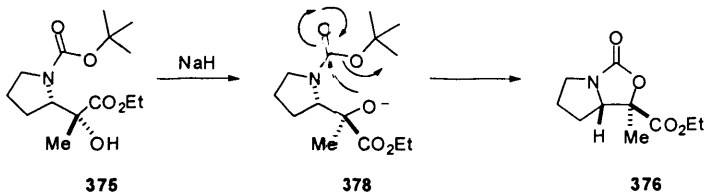
Entry	Conditions	Yield
1	NaH (1 eq), BnBr (1 eq), DMF, rt, 3 h	Mixture
2	Benzyltrichloroacetimidate (1.2 eq), PPTS (0.1 eq), Et_2O, 50 °C,18 h	No reaction
3	NaH (1 eq), BnBr (1 eq), *n*-Bu_4NI, CH_2Cl_2, rt	By-products
4	MOMCl (2 eq), *i*-Pr_2NEt (2 eq), THF, 80°C, 3 days	No reaction
5	TBDPSCl (2 eq), imidazole (1.1 eq), DMF, rt, 24 h	No reaction
6	TBDMSCl (2 eq), imidazole (1.1 eq), DMF, rt, 24 h	No reaction

Treatment of alcohol **375** with NaH and BnBr (entry 1) led to a complex mixture of unidentified compounds. However when *n*-Bu_4NI was added to the reaction mixture (entry 3), we isolated an inseparable mixture of carbamates **376** and **377** as shown in Scheme 91.



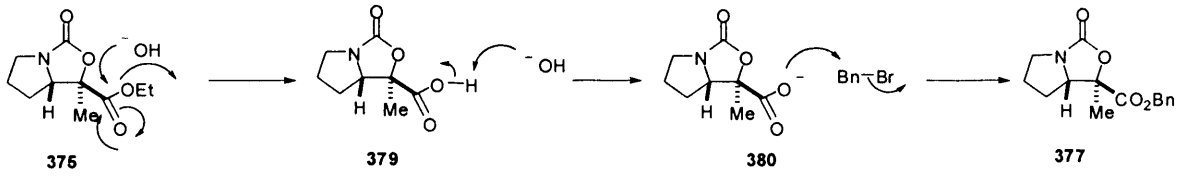
Scheme 91. Protection of alcohol **375**

The carbamate formation could be easily explained by nucleophilic addition of the alkoxide to the carbonyl group of the Boc as illustrated in Scheme 92.



Scheme 92. Formation of carbamate **376**

Formation of the transesterification product was much more surprising as we are under basic conditions. Saponification of the ester might occur if the medium is not completely dry, the resulting carboxylate would then attack BnBr to form **377**.

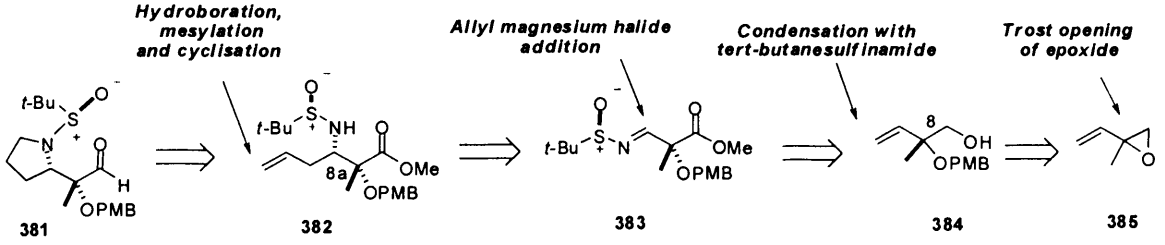


Scheme 93. Formation of carbamate **377**

In light of the collective problems we experienced in this route, we eventually decided to investigate an alternative method for securing the α-alkoxyaldehyde.

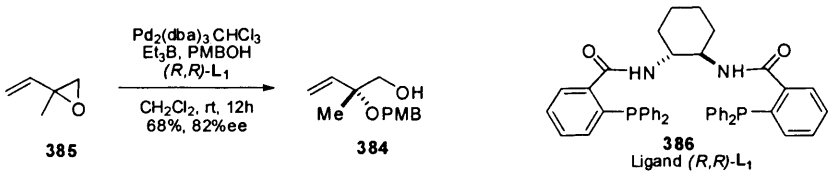
6.2.2. New route for the synthesis of the α-alkoxyaldehyde

In light of these difficulties, we then explored a completely new strategy to synthesise the targeted α-alkoxyaldehyde, and again, our goal was to avoid the use of L-proline. This strategy would install one stereocenter at a time as depicted in Scheme 94. Aldehyde **381** would originate from linear alkene **382** *via* a 3-step sequence. We would utilise the chiral induction of *tert*-butyl sulfinimine **383** to introduce the (C8a) stereocenter of **382** through an addition of an allyl magnesium halide. The sulfinyl group not only would play the role of a chiral auxiliary, but would then be used as a protecting group for the nitrogen. In fact, the sulfinyl group can be removed with TFA like a Boc protecting group. The C(8) stereocenter would be delivered at the first step of the synthesis using a Trost opening of epoxide **385**. With due modification, these disconnections would potentially give us the flexibility to synthesise the α-alkoxyaldehyde with different substituents on the 5 membered-ring.



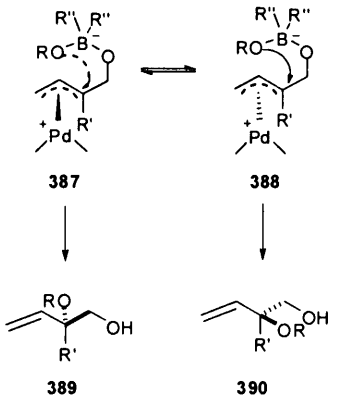
Scheme 94. New retrosynthetic plan to α-alkoxyaldehyde

The synthesis started with a chemo-, regio- and enantioselective addition of *p*-methoxybenzylalcohol to the commercially available racemic isoprene oxide **385**. This deracemization reaction, originally described by Trost and co-workers, was achieved using 0.01 equiv of $Pd_2(dba)_3.CHCl_3$, 0.01 equiv of triethyl borate, 0.01 equiv of chiral ligand **386** and 1 equiv of PMB-OH[97] (Scheme 95).



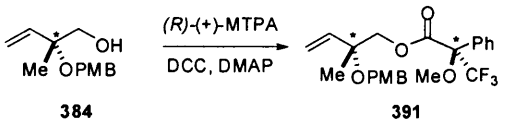
Scheme 95. The Trost opening of epoxide **385**

Many factors come into play for the addition to be chemo-, regio- and enantioselective as summarised in Scheme 96. In the absence of Et_3B, attack of a nucleophile would occur at the less hindered end of the π-allylpalladium intermediate. The first role of the triethylborane is to control the regioselectivity. Secondly, Et_3B enhances the nucleophilicity of the alcohol, which is normally a poor nucleophile, and finally, Et_3B controls the chemoselectivity of the reaction. In fact, the product primary alcohol does not react after its formation. Finally, for the reaction to be enantioselective, the diastereomeric interconversion of the π-allylpalladium intermediates must be faster than the alkoxide attack. This issue is controlled by the palladium catalyst and its ligand.



Scheme 96. Mechanism of Trost's reaction

In our case, the addition of *p*-methoxybenzylalcohol proceeded in 68% yield and 82% ee. The enantiomeric excess was determined from the 300 MHz ^{19}F NMR analysis of the Mosher's ester **391**. Alcohol **384** was reacted with the Mosher acid (*R*)-(+)-MTPA in presence of DCC and DMAP in dichloromethane to afford ester **391** (Scheme 97). The diastereoisomeric excess was then easily calculated by integrating the signals from the trifluoromethyl group in the ^{19}F NMR spectrum.[98]

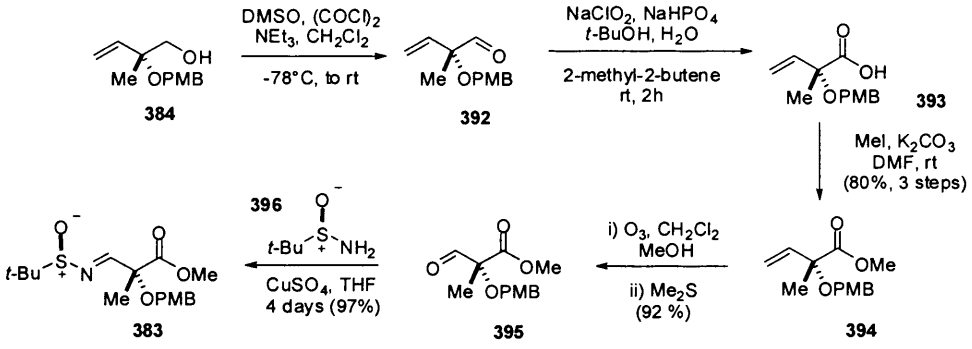


Scheme 97. Synthesis of the Mosher's ester **391**

Alcohol **384** was next oxidised under Swern conditions into the unstable aldehyde **392** (Scheme 98). After rapid purification by SiO_2 flash chromatography, the structure of aldehyde **392** was confirmed by its 500 MHz ^1H NMR spectrum that showed a singlet at δ 9.49 ppm due to the aldehyde proton. On normal runs, aldehyde **392** was used crude and converted to the carboxylic acid **393** by Pinnick addition using sodium chlorite in the presence of NaH_2PO_4 and 2-methyl-2-butene to act as a chlorine scavenger.[99] Again, acid **393** was purified only for analytical purpose as it could be used crude for the next step. Evidence for the success of this reaction was given by the presence of a very broad OH band that overlapped with the CH band around 3250 cm^{-1} in the infra-red spectrum of acid **393**. Furthermore, 500 MHz ^1H NMR analysis

in $CDCl_3$ showed the disappearance of the aldehyde hydrogen previously at δ 9.49 ppm. Treatment of the crude acid with MeI and K_2CO_3 in DMF afforded ester **394** which was purified by SiO_2 flash chromatography. The combined three-step sequence was easily implemented on a large scale since it only required purification at the last step, ester **394** being obtained pure in a very good yield (80%) over the 3 steps.

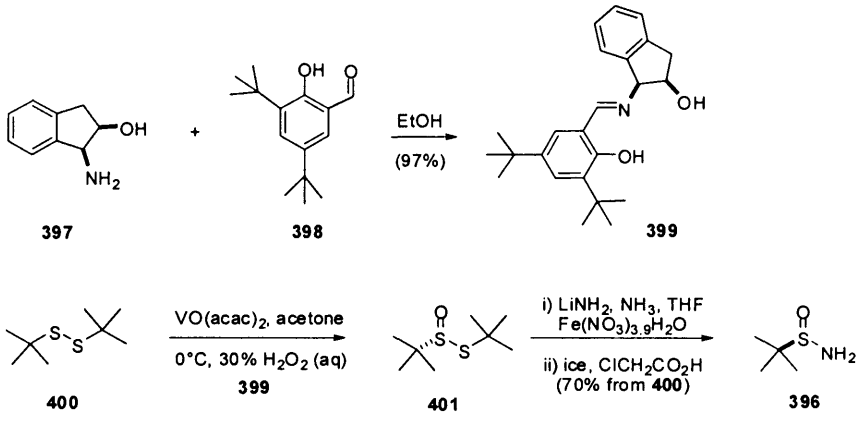
Ozonolysis of the double bond led to aldehyde **395** in 92% yield, as evidenced by the presence of a singlet at δ 9.64 ppm in the 500 MHz ^{1}H NMR spectrum of the isolated product. Aldehyde **395** was condensed in dichloromethane with chiral *(R)-tert*-butylsulfinamide **396** in presence of anhydrous copper sulfate to afford *(R)-tert*-butanesulfinyl imine **383** in a very good yield.[100] Copper sulfate is an excellent promoter of this reaction; it acts both as a Lewis acid and as a drying agent. Importantly, the work-up of this reaction was very easy; the reaction mixture was filtered through a pad of silica, the filtrate was concentrated *in vacuo* to afford the pure sulfinyl imine **383**. The success of this conversion was apparent from the presence of the imine proton at δ 8.17 ppm in the 500 MHz ^{1}H NMR spectrum of **383** in $CDCl_3$.



Scheme 98. Synthesis of sulfinylimine **383**

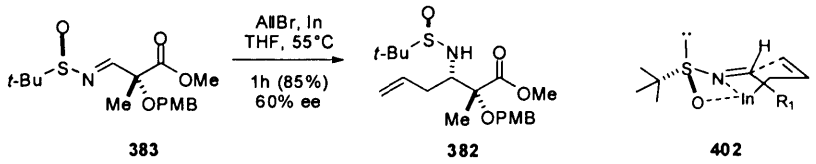
Chiral *(R)-tert*-butanesulfinamide **396** is commercially available. However, it is very expensive and can be prepared easily on a large scale following Ellman's procedure[101](Scheme 99). First, chiral ligand **399** is made by mixing 1 equivalent of (1*S*,2*R*)-(-)-cis-1-amino-2- indanol **397** with 1 equivalent of 3,5-di-tert-butyl salicylaldehyde **398** in EtOH. The ligand is obtained as a yellow solid after evaporation of EtOH. *(R)-tert*-butanesulfinamide is then prepared in two steps from *tert*-butyl disulfide **400**. A catalytic asymmetric oxidation of the *tert*-butyl disulfide

using hydrogen peroxide and catalytic amount of vanadium(IV) acetylacetonate in the presence of chiral ligand **399** affords the (*S*)-*t*-butyl-*t*-butanethiosulfinate **401**. Hydrogen peroxide must be added in a very slow, steady stream at 0 °C. The course of the reaction was conveniently followed by 500 MHz ^{1}H NMR. Following extraction with dichloromethane, crude **401** is added to a solution of lithium amide in liquid ammonia to afford *(R)-tert*-butanesulfinamide **396**. We were able to conduct this procedure on 20 g scale.



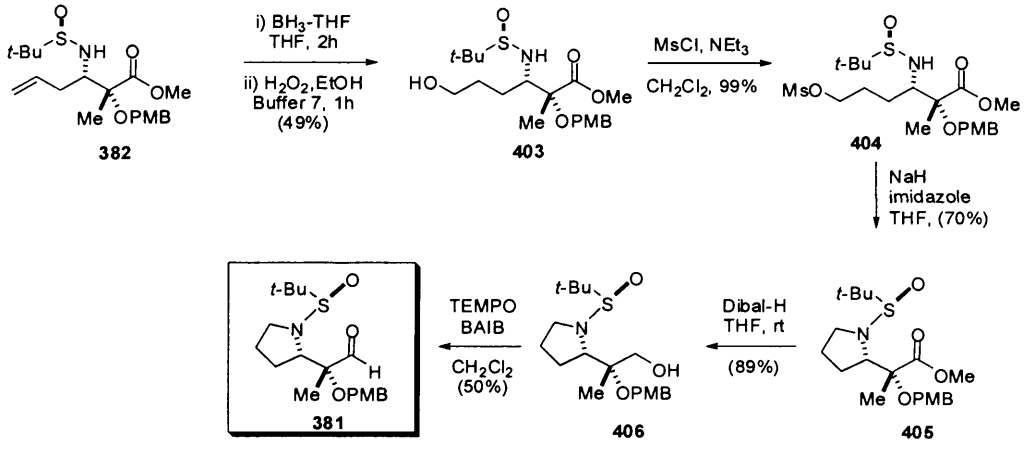
Scheme 99. Synthesis of *(R)-tert*-butanesulfinamide **396**

With imine **383** in hand, our initial plan was to synthesise the homoallylic sulfinamide **382** using the addition of an allylmagnesium halide. Despite this reaction being widely described in the literature,[102] when we added allylmagnesium bromide to *tert*-butanesulfinylimine **383**, a very low yield of **382** was obtained. After some literature searching, we found a very interesting paper from Foubelo and Yus who reported the indium-mediated addition of allyl bromides to *tert*-butanesulfinylimine.[103] Their conditions were applied to our substrate and to our delight the indium-mediated addition of allyl bromide to sulfinyl imime **383** took place smoothly at 60°C, using 1.3 equiv of In and 1.3 equiv of AllBr in THF. The homoallylic sulfinamide **382** was obtained in 85% after purification by SiO_2 flash chromatography. The diastereomeric ratio of the reaction was found to be 80:20, as determined by 500 MHz ^{1}H NMR spectroscopy in $CDCl_3$. It can be explained by a chair like transition state. The reactivity of the electrophilic centre of the imine is increased by coordination of the indium to nitrogen while coordination to the oxygen of the sulfinyl group is responsible for the face selectivity (Scheme 100).



Scheme 100. Indium-mediated addition of allyl bromide

The diastereoisomers could not be separated at this stage and the hydroboration reaction was next investigated on the mixture enriched in olefin **382**. The use of pinacol borane, catechol borane and 9 BBN was unsuccessful. We believe that this lack of reactivity is attributable to the steric hindrance of the *(R)-N*-tert-butanesulfinamide group. Therefore, the reaction was achieved using the less hindered BH_3-THF complex (Scheme 101). A complex mixture of compounds was formed, from which alcohol **403** was isolated in 40% yield for the two steps from sulfinyl imine **383**. Evidence for the success of this reaction was provided by the appearance of an OH stretching band at 3333 cm^{-1} in the infra-red spectrum of alcohol **403**. Moreover, 500 MHz ^1H NMR analysis in $CDCl_3$ showed disappearance of the olefinic protons at δ 5.71 and 4.97 ppm. *O*-Mesylation was then accomplished in a nearly quantitative yield using MsCl and NEt_3. The structure of mesylate **404** was confirmed by the appearance of a singlet at δ 2.93 ppm in the 500 MHz ^1H NMR spectrum of **404** in $CDCl_3$.



Scheme 101. Synthesis of α-alkoxyaldehyde **381**

Cyclisation did occur in the presence of NaH/imidazole which permitted internal nucleophilic displacement in 72% yield. Proof of the cyclisation was provided by the 125 MHz 2D NMR-HMBC experiment in $CDCl_3$ that showed the long range ^{1}H-^{13}C couplings (Figure 20). Specifically, a coupling was observed between carbon 3 and the proton α to the nitrogen.

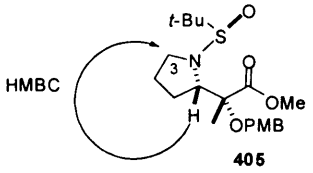
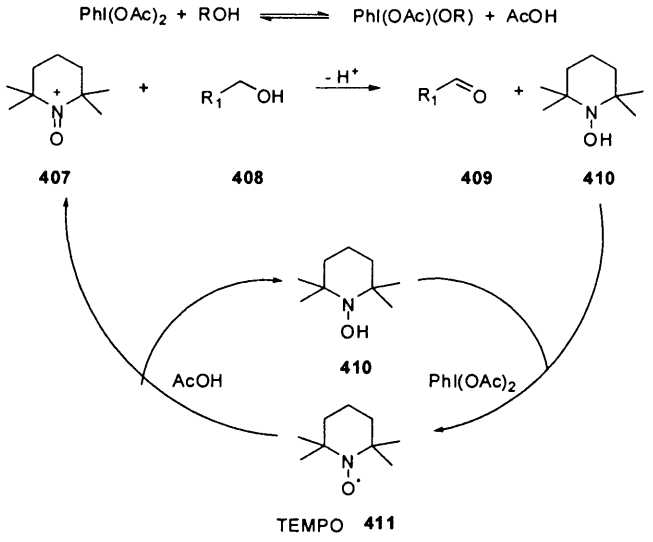


Figure 20. The long range ^{1}H-^{13}C couplings in **405**

Finally, ester **405** was reduced with DIBAL-H to alcohol **406**. Success was confirmed by the OH stretching band at 3391 cm^{-1} in its infra-red spectrum. Attempts to oxidise alcohol **405** into the desired aldehyde failed using PCC; TPAP/NMO gave an incomplete reaction according to TLC. Eventually, the oxidation was achieved using [bis(acetoxy)iodo]benzene (BAIB) in presence of catalytic amount of TEMPO;[104] it provided the desired α-alkoxyaldehyde **381** in 50% yield. The oxidising agent is the oxaammonium salt **407** resulting from the dismutation of TEMPO **411** in the presence of acetic acid (Scheme 102). The catalytic amount of acetic acid needed for the dismutation to occur arises from a ligand exchange around the iodide atom. TEMPO **411** is regenerated from hydroxylamine **410** by action of BAIB.



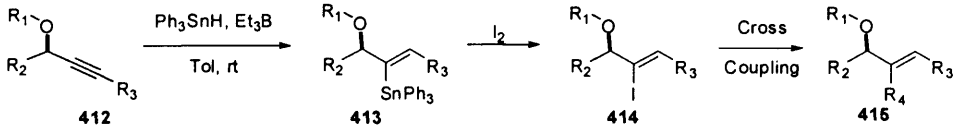
Scheme 102. Mechanism of alcohol oxidation using TEMPO/BAIB

The structure of aldehyde **381** was confirmed by its 500 MHz ^{1}H NMR spectrum in $CDCl_3$ that showed a singlet at δ 9.68 ppm.

6.3. Synthetic Studies Towards The Side Chain Segment

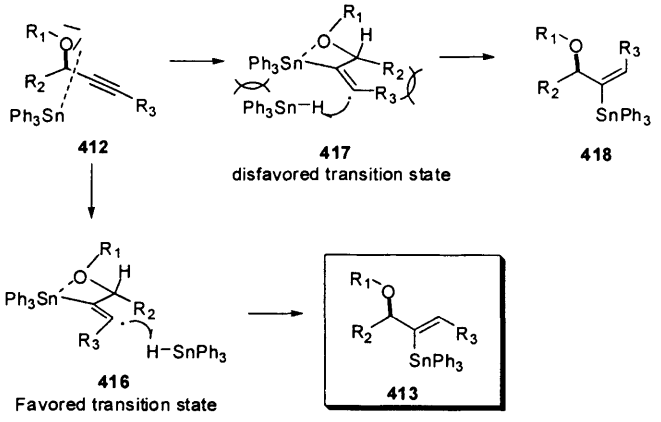
6.3.1. The *O*-Directed Free-Radical Hydrostannation of Propargyl Ethers, Acetals and Alcohols

Our synthesis of the side chain aldehyde segment **270** would utilise the recently developed *O*-directed free-radical hydrostannation of disubstituted alkynes for stereodefined alkene construction[105,106] (Scheme 103). In this methodology, vinyl triphenylstannanes **413** are obtained in a regio- and stereoselective manner from disubstituted propargylic allyl oxygenated alkylacetylenes **412**. The vinyl triphenylstannanes **413** are usually readily manipulated into trisubstituted alkenes with complete retention of olefin geometry following a tin-iodide exchange and transition metal catalysed cross-coupling.[107]



Scheme 103. The *O*-directed hydrostanation and the subsequent elaboration of trisubstituted alkenes

The procedure utilises 1.5 eq of Ph_3SnH and 0.1 eq of Et_3B in toluene at 0.1 M concentration with respect to the starting alkene. Coordination of Ph_3SnH to the *O*-atom of the acetylene and subsequent H-atom abstraction and radical attack of the alkyne lead to two possible transition invertomers **416** and **417**. Scheme 104 shows that great steric hindrance would operate in the transition state **417** in the vinyl radical H-atom abstraction step. In the transition state **416**, however, the minimized steric repulsions preferentially lead to the formation of **413**.



Scheme 104. Transition states of the *O*-directed free radical hydrostannation

The previously reported *O*-directed free-radical hydrostannation employing Bu_3SnH is much less effective. This can be explained by two reasons. First, the electron-withdrawing phenyl group enhances the Lewis acidity of the tin atom, and secondly, greater steric effects favour the **416** transition state.

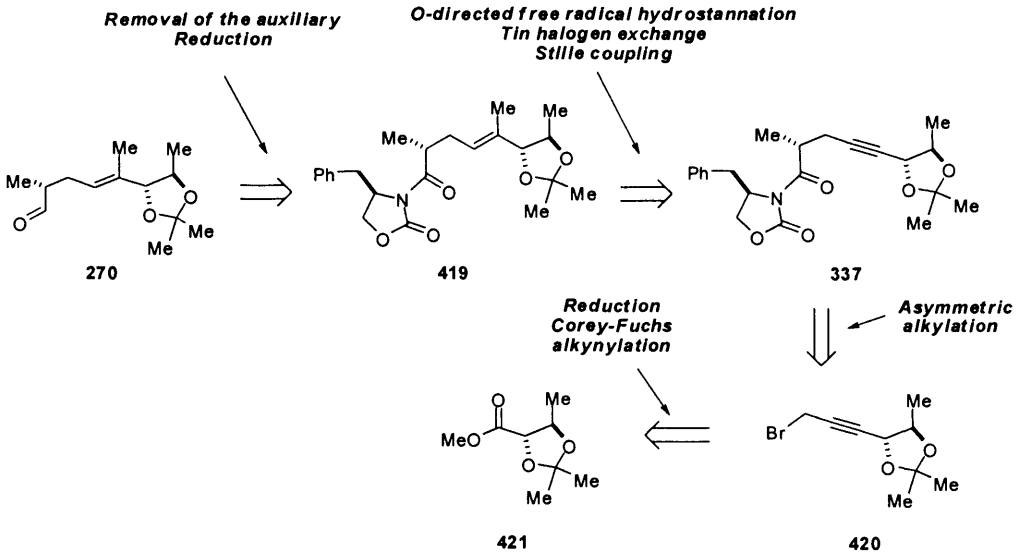
Our group has demonstrated that the vinyltriphenylstannane products **413** can readily undergo tin-halogen exchange with retention of configuration.[107] The reaction outcome was not as predictable as it might at first sight appear. In fact, past literature shows many examples

where the iododemetallation of β-vinyltriphenylstannanes with an allylic *O*-substituent (that could coordinate) could lead to replacement of one the phenyl groups by the iodide atom. However, X-ray crystallography of many vinyltriphenylstannanes of structure **414** later showed that O-coordination does not occur in these systems; hence the "normal" outcome.

Finally, the resulting vinyl iodides can readily be converted into trisubstituted alkenes through a range of Pd (0) catalyzed cross-coupling techniques.

6.3.2. Retrosynthetic plan

Returning to our allopumiliotoxin 339A synthesis, aldehyde **270** would be prepared from oxazolidinone **419**. Trisubstituted alkene **419** appeared derivable from alkyne **337** using the previously described methodology. This would give us great flexibility regarding the substituent on the trisubstituted alkene. The C(11) stereocenter would be installed in an asymmetric alkylation with bromide **420** using the induction of a chiral auxiliary. Bromide **420** would itself be prepared from ester **421** through reduction into the aldehyde followed by a modified Corey-Fuchs alkynylation (Scheme 105).

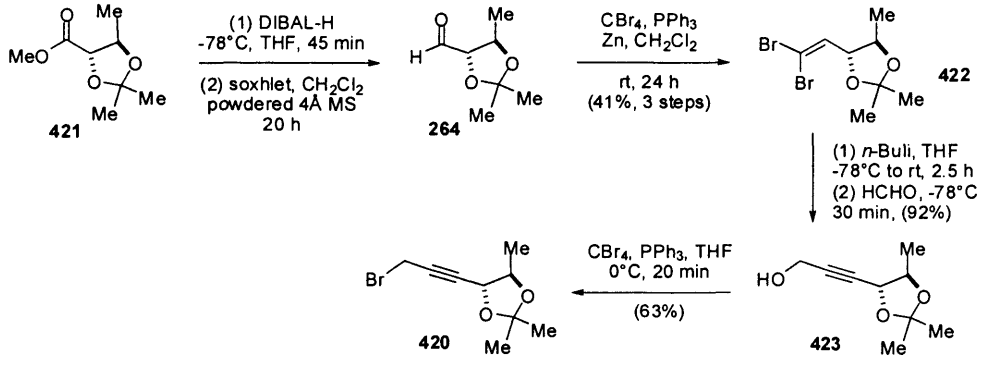


Scheme 105. Our retrosynthetic analysis of the side chain segment of (+)-allopumiliotoxin 339A

6.3.2. Implementation of the Retrosynthetic Strategy for the Side Chain Segment of (+)-Allopumiliotoxin 339A

Despite ester **421** being commercially available, it is very expensive. It was thus prepared on a large scale from L-threonine in 41% yield according to Servi procedure.[108] Kirschning and coworkers published a synthesis of dibromide **422** from ester **421**.[109] Unfortunately, very low yields were obtained when we followed this protocol. This is probably because reduction of ester **421** led to a mixture of aldehyde **264** and its hydrate.[110] We modified their procedure by adding a dehydration step. The crude mixture obtained from the DIBAL-H reduction of ester **421** was dehydrated in CH_2Cl_2 at reflux using a Sohxlet extractor containing 4Å activated molecular sieves for water removal. The resulting solution was then added to a mixture of CBr_4 (2 eq), PPh_3 (2 eq) and Zn (2 eq) in dichloromethane. After removal of the triphenylphosphine oxide, dibromide **422** was obtained in 41% yield from ester **421** after purification by SiO_2 flash chromatography. Analysis by IR and NMR spectroscopy was in accordance with the data published by Kirschning. Dibromide **422** was then converted to the propargyl alcohol **423** using *n*-butyllithium and paraformaldehyde in THF at -78 °C. TLC analysis showed complete disappearance of starting material and the appearance of a single spot. As the alcohol was very unstable, it was not possible to carry out all the characterisation. It was usually used straight

after purification. Nevertheless, evidence for its formation was given by the disappearance of the ethylenic proton at δ 6.49 ppm in the 500 MHz ^{1}H NMR spectrum in $CDCl_3$. Subsequent treatment with CBr_4 and PPh_3 in THF at 0°C provided bromide **424** in 63% yield. Again, because of the instability of the bromide, a full characterisation could not be achieved. It is noteworthy that dibromide **422**, propargylic alcohol **423** and bromide **424** are all very sensitive and can not be stored without appreciable losses. Their immediate use is therefore recommended.



Scheme 106. Synthesis of bromide **420**

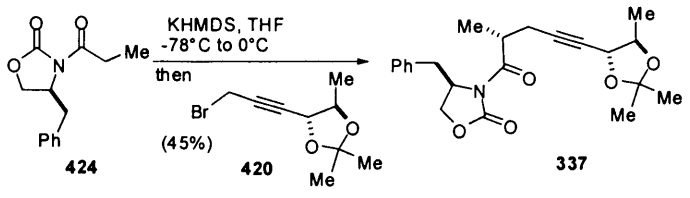
We next explored a variety of conditions to achieve the Evans alkylation between bromide **420** and oxazolidinone **424** (Table 2).

Table 2.

Entry	Conditions	Yield
1	KHMDS (1.3 eq), THF, -78 °C, 1 h	45%
2	KHMDS (1.3 eq), HMPA (5 eq), THF, -78 °C to 0 °C, 2 h	degradation
3	LDA (1.1 eq), THF, -78 °C overnight	15%
4	*n*-BuLi (1.1 eq), THF, -78 °C overnight	No reaction

Use of lithium hexamethyldisilazide as a base (entry 1) gave the best result providing alkyne **337** in a very moderate 45% yield (Scheme 107). When HMPA was added to the

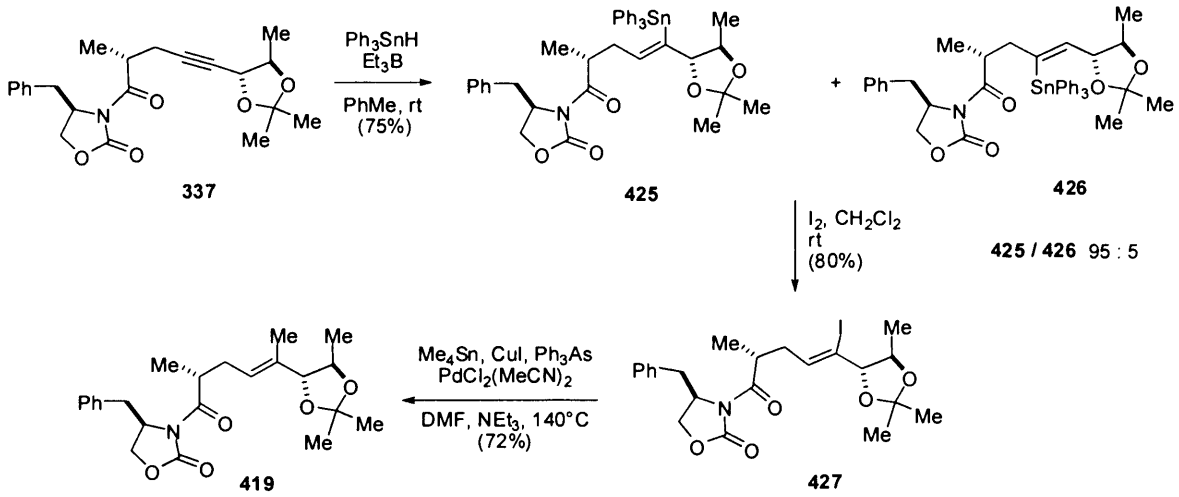
reaction mixture, degradation occurred (entry 2). Using LDA as a base (entry 3) afforded **337** in a very poor yield (15%), and *n*-BuLi left the starting material untouched (entry 4).



Scheme 107. Evans alkylation of oxazolidinone **424** with bromide **420**

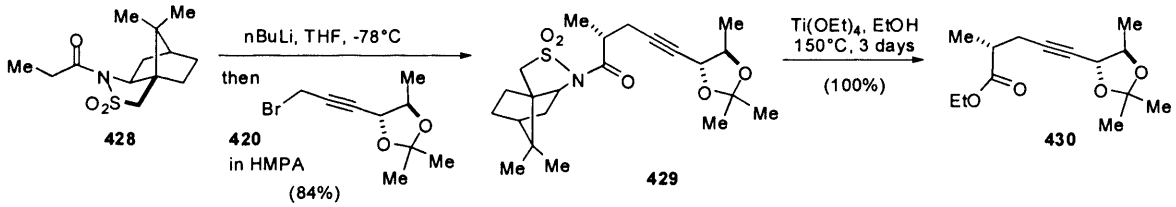
We next investigated the feasibility of stereoselectively transforming acetylene **337** into trisubstituted olefin **419**.[105,107] The *O*-directed free-radical hydrostannation was achieved successfully in 75% yield using Ph_3SnH and Et_3B in toluene (Scheme 108). 500 MHz NMR analysis of the product in $CDCl_3$ showed that a mixture of isomers in ratio 95:5 was obtained. The structure of the major isomer **425** was confirmed by an apparent triplet at δ 6.60 ppm, showing that stannation had occurred at the carbon α to the oxygen. The minor isomer was believed to be **426** even though no characterisation was possible.

The iododestannation proceeded with complete preservation of olefin geometry in 80% yield. Finally, a Stille coupling with Me_4Sn afforded the trisubstituted alkene **419** in 72% yield. Evidence for the success of this reaction was given by the appearance of a singlet at δ 1.63 ppm, integrating for 3 protons in the 500 MHz ^1H NMR spectrum in $CDCl_3$. Moreover, the olefinic proton was deshielded from δ 6.14 ppm for the vinyl iodide to δ 5.53 ppm for the trisubstituted alkene.



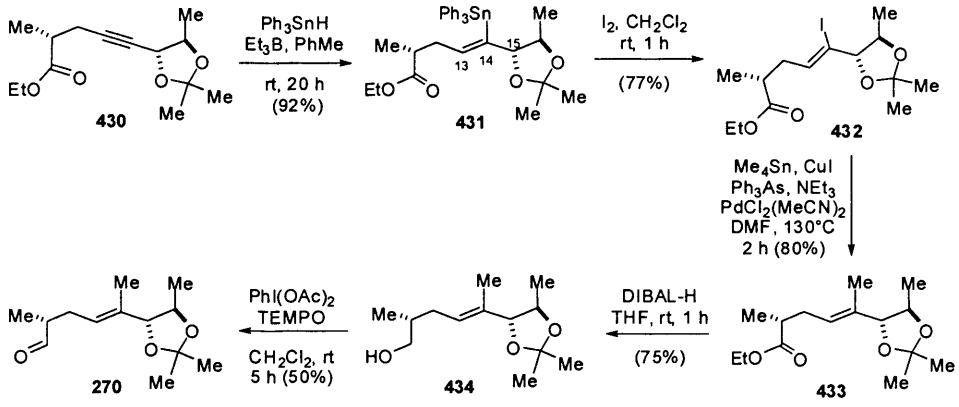
Scheme 108. Synthesis of trisubstituted alkene **419**

These last 3 steps showed us the feasibility of this methodology on this kind of substrates but the low yield for the alkylation reaction led us to abandon the use of the Evans auxiliary. Instead we investigated the alkylation reaction using Oppolzer's camphorsultam auxiliary. This strategy turned out to be successful as treatment of *N*-propionylsultam **428** with *n*-butyllithium followed by bromide **420** in HMPA proceeded in 90% yield.[111] The camphor sultam auxiliary was then removed under very mild conditions by means of a titanium-mediated transesterification.[112,113] Exposure of adduct **429** to 10 equiv of $Ti(OEt)_4$ in ethanol at reflux led to ester **430** in a quantitative yield along with 96% of the recovered sultam. This reaction was extremely convenient as it led directly to the ester. Indeed the other methods to remove the sultam auxiliary led either to the carboxylic acid (LiOH, H_2O_2) or to the secondary alcohol ($LiAlH_4$). Moreover, it was very easy to separate the auxiliary from the ester because of the difference of polarity of these two molecules. In fact, on TLC, the ester was the fast moving product and the auxiliary stayed close to the baseline. When comparing the infra-red spectra of the starting material and of the product ester, it was clear that the stretching band of the C=O moved from 1697 cm^{-1} for the amide to 1736 cm^{-1} for the ester (Scheme 109).



Scheme 109. Synthesis of propargyl acetal **430**

We next addressed the *O*-directed free-radical hydrostannation of propargyl acetal **430**. We were very pleased to find out that the reaction proceeded in a very good yield using 2 eq of Ph_3SnH and 3 eq of Et_3B in toluene (Scheme 110). Vinylstannane **431** was obtained as a single diastereoisomer in 92% yield. Confirmation that the stannation occurred at the carbon α to the oxygen was assessed by 500 MHz ^1H NMR analysis of **431** in $CDCl_3$, which showed the olefinic proton as a ddd at δ 6.55 ppm. Furthermore, the vinylic proton (H13) showed a ^1H-^{117}Sn coupling constant of 150 Hz which is the expected value for this geometry.



Scheme 110. Synthesis of aldehyde **270**

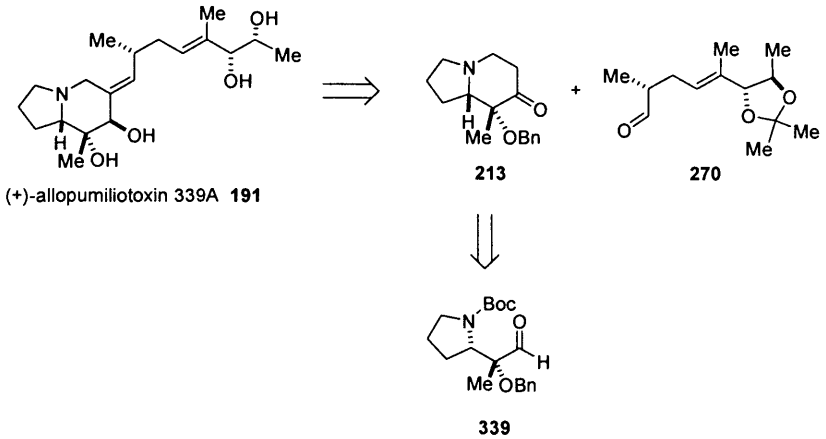
Subsequent tin-halogen exchange furnished iodide **432** in 77% yield. The success of this conversion was apparent from the absence of any aromatic protons in the 500 MHz NMR spectrum of **432** in $CDCl_3$. Once again, the formation of the iodo(diphenyl)stannylidene was not detected. A Pd(0)-mediated Stille coupling was successfully performed in the presence of copper(I) iodide and triphenylarsine in DMF at 140°C and trisubstituted alkene **433** was

obtained in 72% yield. Evidence for the success of this reaction was given by the appearance of a singlet at δ 1.63 ppm integrating for 3 protons in the 500 NHz ^{1}H NMR spectrum of **433** in $CDCl_3$. Moreover, the olefinic proton was deshielded from δ 6.07 ppm for the vinyl iodide to δ 5.45 ppm for the trisubstituted alkene.

DIBAL-H reduction afforded alcohol **434** in 75% yield as evidenced by the appearance of a broad OH stretching band at 3433 cm^{-1} in the infra-red spectrum of **434**. Oxidation of the alcohol into aldehyde **370** was achieved in 50% yield using $PhI(OAc)_2$/TEMPO oxidation.[104] The success of the oxidation was apparent from the presence of a singlet at δ 9.64 ppm in the 500 MHz ^{1}H NMR spectrum in $CDCl_3$.

7. Conclusion and future work

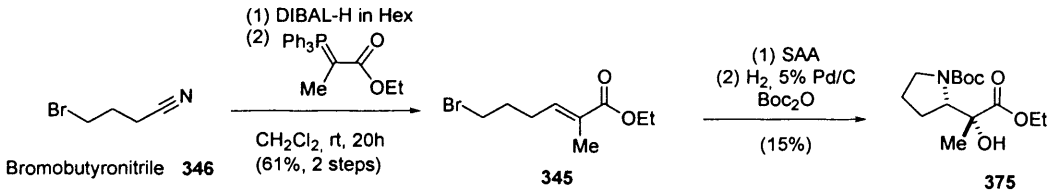
The initial goal of this work was to achieve the total synthesis of (+)-allopumiliotoxin 339A. The latter shows marked cardiotonic and myotonic activity. Our retrosynthetic plan was based on the synthesis of α-alkoxyaldehyde **339** and a side chain aldehyde **270** containing a trisubsituted alkene as summarised in Scheme 111.



Scheme 111. Retrosynthetic analysis of (+)-allopumiliotoxin 339A

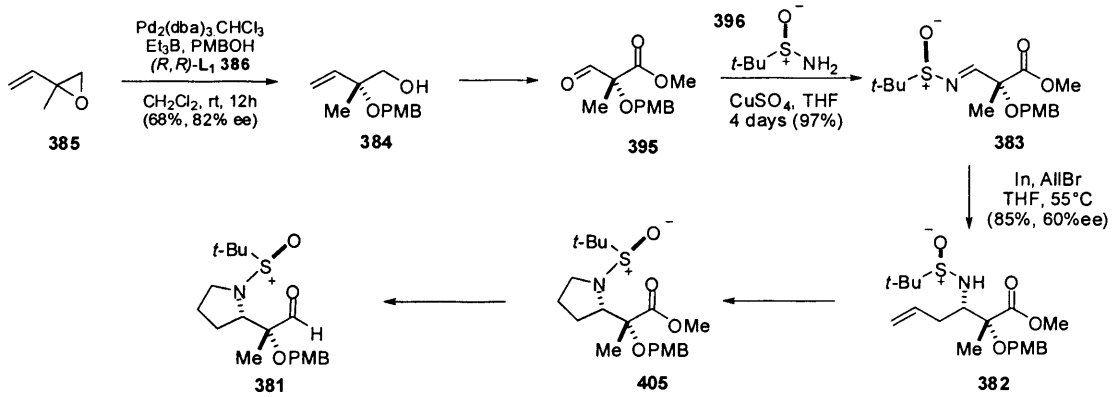
Our initial efforts focused on the synthesis of α-alkoxyaldehyde **339** using a Sharpless Asymmetric Aminohydroxylation (SAA). A four-step route was developed to α-alkoxyester **375**

from bromobutyronitrile **346** (Scheme 112). The key reaction was the SAA which allowed to install two stereocenters and to close the nitrogen 5 membered ring in only one step. However a very low yield was obtained and difficulties were encountered to protect alcohol **375**.



Scheme 112. Synthesis of α-alkoxyester **375**

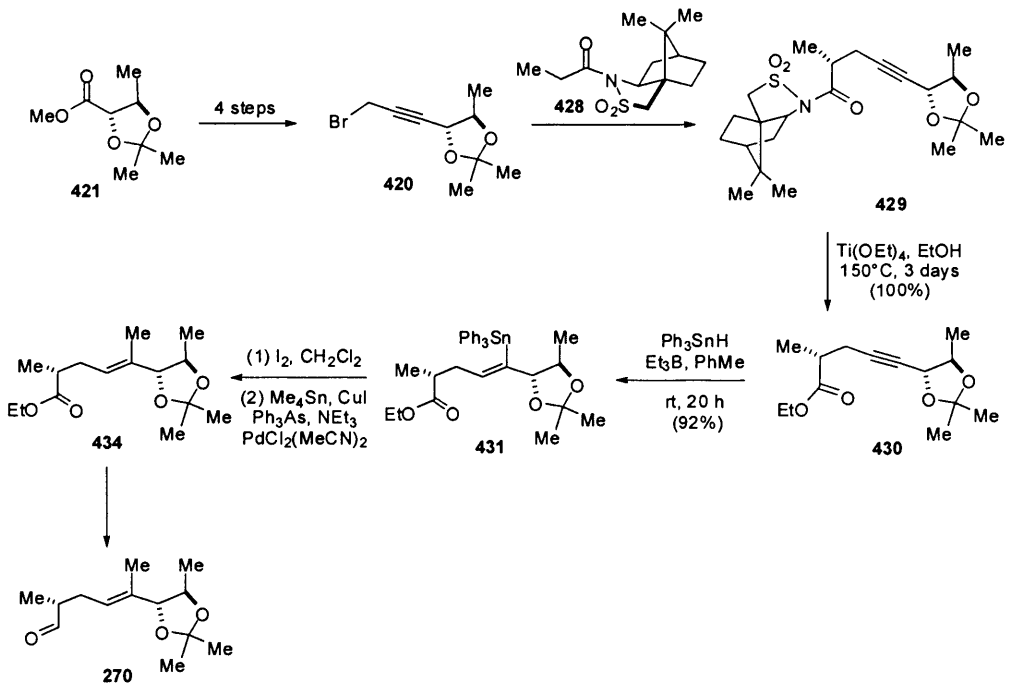
The second approach to α-alkoxyaldehyde **381** was based on two key steps (Scheme 113). First a Trost's opening of racemic aldehyde **385** afforded alcohol **384** which was converted in 4 steps to aldehyde **395**. Secondly, attachment of chiral (*R*)-tert-butanesulfinamide **396** to aldehyde **395** using copper sulfate afforded chiral sulfinylimine **382**. It allowed to install the second stereocenter *via* an asymmetric indium-mediated addition of allylbromide. Compound **382** was converted to ester **405** after hydroboration, activation of the resulting alcohol and base mediated cyclisation. Eventually ester **405** was converted to aldehyde **381**. α-Alkoxyaldehyde **381** was synthesised in 6% overall yield over 12 steps.



Scheme 113. . Synthesis of α-alkoxyaldehyde **381**

The synthesis of the side chain aldehyde **270** is summarised in Scheme 114 and started from methyl ester **421** which was converted into bromide **420** in 4 steps. An asymmetric

alkylation of bromide **420** with compound **428** afforded alkyne **429**. After removal of the sultam auxiliary, alkyne **430** underwent the *O*-directed free-radical hydrostannation reaction in very good yield to afford stannane **431** as a single isomer. Conversion to trisubstituted alkene **434** was achieved *via* tin halogen exchange followed by Stille coupling. Finally ester **434** was converted to aldehyde **270** in 2 steps. The side chain aldehyde **270** was prepared in 4.2% overall yield over 12 steps from ester **421**.



Scheme 114. Synthesis of side chain aldehyde **270**

We have developed syntheses of two precursors needed in our designed route to (+)-allopumiliotoxin 339A. The strength of these routes is their flexibility. In fact, the avoidance of L-proline in the α-alkoxyaldehyde **381** synthesis would allow us to anchor substituents on the 5 membered-ring or even to build a 6 membered-ring. Furthermore, we proved the great utility of the *O*-directed free-radical hydrostannation reaction of disubstituted alkynes with Ph_3SnH and Et_3B; using this method, we could easily modify the substituent on the trisubstituted alkene.

PART C: EXPERIMENTAL

All starting materials were obtained commercially from Aldrich, Acros, Avocado, Lancaster or BDH. Reactions were carried out under a nitrogen atmosphere with freshly distilled solvents unless otherwise stated. All solvents were reagent grade. Dichloromethane, benzene and acetonitrile were distilled from calcium hydride under nitrogen. Diethyl ether and THF were distilled from sodium under nitrogen. Where petrol is specified this refers to the fraction that boils in the range 40-60 °C. 4-Toluensulfonyl chloride was recrystallised from chloroform/petrol prior to use. All other reagents were used as supplied from the manufacturer.

Reactions carried out at - 78 °C were cooled by means of an acetone/dry ice bath, those at - 10 °C by means of an ice/salt/water bath and those at 0 °C by means of an ice/water bath.

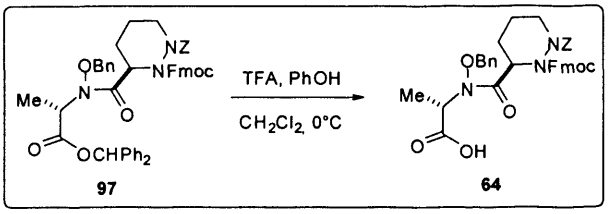
Flash column column chromatography was carried out on Kieselgel 60 40/60A (220-240 mesh) silica gel. TLC was carried out on pre-coated glass-backed plates (Merck Kieselgel 60 F_{254}), visualised at 254 nm and stained with either of anisaldehyde, iodine, or PMA.

Infrared spectra (IR) were recorded on a SHIMADZU FT-IR 8700 using potassium bromide (neat) disc. The wave number is given in cm^{-1} with intensity strong = s, medium = m, weak = w. Optical rotations were measured on an Optical Activity, Polaar 2000 automatic polarimeter. Mass measurements were recorded by Mr John Hill or Dr Lisa Harris of the Christopher Ingold Laboratories on a VG70-SE (CI^+, EI^+, FAB^+).

Proton Nuclear Magnetic Resonance spectra (^1H NMR) were recorded on a Bruker AMX-500 NMR Spectrometer at 500 MHz or on a Bruker AMX-400 NMR Spectrometer at 400 MHz. ^{13}C NMR were recorded at 125 MHz. The NMR spectra were recorded with reference to the solvent peak ($CHCl_3$ in $CDCl_3$ at 7.24 ppm for ^1H NMR and 77.0 ppm for ^{13}C NMR). ^{13}C DEPT (CH and CH_3 positive and CH_2 negative) was also used to assign ^{13}C NMR. HMQC (proton-carbon coupling) and HMBC (proton-carbon long range coupling) were used to determined structures. The signals are noted as s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, t = triplet,q = quadruplet, dt = doublet of triplet, tt = triplet of triplet, tq = triplet of quadruplet, m = multiplet and br = broad. Coupling constants *J* are reported in Hz

8. Synthetic studies on Molecules Related to the Azinothricin Family

Acid 64



To ester **97**[114] (11.43 g, 0.0138 mol) in dry CH_2Cl_2 (150 mL) at 0 °C under N_2 was added PhOH (1.85 g, 0.197 mol) and TFA (38 mL, 0.496 mol). The reaction mixture was stirred at 0 °C for 3 h and then concentrated *in vacuo*. The residue was co-evaporated from toluene (50 mL x 3). The crude residue was purified by SiO_2 flash chromatography (gradient elution 5:1 to 2:1 petrol:EtOAc) to give acid **64** as a white foam (8.34 g, 91%).

IR (neat) 3160 (br), 3065 (w), 2951 (m), 1715 (s, br), 1450 (s), 1412 (s), 1358 (m), 1296 (s), 1257 (s), 1196 (s), 1124 (m), 1090 (m), 1051 (w), 970 (w), 912 (w), 883 (w), 741 (s), 700 (m).

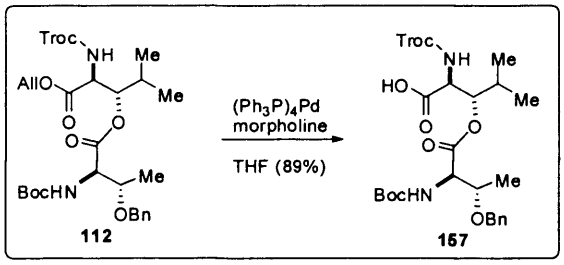
^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 7.74-7.13 (m, br, Ar), 6.0 (s, br), 5.47 (m, br), 5.22-4.77 (m, br), 4.73-4.46 (m, br), 4.31 (s, br), 4.21-3.96 (m, br), 2.86 (m, br), 2.33 (s, br), 2.20 (s, br), 1.84-1.61 (m, br), 1.50-1.38 (m, br), 1.25 (s, br).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 174.0, 172.6, 155.4, 143.8, 143.1, 141.3, 136.2, 134.0, 129.6-126.4 (Ar), 125.1, 120.0, 68.7, 68.3, 67.8, 50.5, 49.9, 47.0, 46.9, 45.6, 44.0, 29.7, 23.9, 23.1, 19.3, 18.6, 14.2.

FAB (+) HRMS: Calcd. for $C_{38}H_{38}N_2O_8$: $(M+H)^+$: *m/e* 664.26588; Found: *m/e* 664.26409.

The spectral data for this molecule corresponded with that in literature.[36]

Acid 157



To a solution of ester **112**[24] (7.64 g, 11.7 mmol) in THF (46 mL) at rt, under N_2, was added morpholine (8.0 mL, 93.5 mmol) and tetrakis(triphenylphosphine) palladium (1.35 g, 1.17 mmol). The reaction mixture was stirred at rt for 30 min, diluted with ether (40 mL) and washed with 1 M aq. $KHSO_4$ (2 x 60 mL) and brine (40 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The product was purified by SiO_2 flash chromatography (gradient elution 4:1 to 1:2 petrol:EtOAc) affording the title compound **157** as a yellow foam (6.37 g, 89%).

IR (neat) 3327 (br), 2979 (m), 1728 (s), 1508 (m), 1163 (m), 1095 (w), 816 (w), 737 (w), 698 (w)

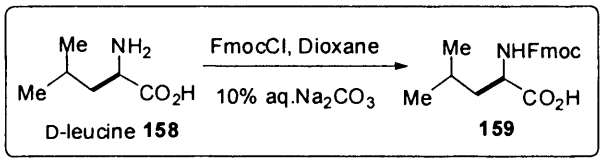
^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 7.34-7.22 (m, 5 H, Ar), 6.53 (d, *J* = 8.7 Hz, 1 H), 5.41 (d, *J* = 9.4 Hz, 1 H), 4.99 (dd, *J* = 8.5, 3.9 Hz, 1 H), 4.71 (d, *J* = 12.2 Hz, 1 H, CH_2O), 4.69 (m, 1 H) 4.62 (d, *J* = 12.2 Hz, 1 H, CH_2O), 4.56 (d, *J* = 11.5 Hz, 1 H, CH_2O), 4.42 (dd, *J* = 9.5, 2.4 Hz, 1 H), 4.37 (d, *J* = 11.5 Hz, 1 H, CH_2O), 4.13 (m, 1 H), 2.21 (m, 1 H), 1.44 (s, 9 H, $(C\underline{H}_3)_3$), 1.25 (d, *J* = 6.2 Hz, 3 H, $CH(C\underline{H}_3)$), 1.05 (d, *J* = 6.9 Hz, 3 H, $CH(C\underline{H}_3)_2$) , 0.87 (d, *J* = 6.9 Hz, 3 H, $CH(C\underline{H}_3)_2$).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 171.0, 170.5, 156.9, 154.1, 137.5, 128.3, 127.7, 127.4, 95.3, 81.0, 80.9, 74.7, 74.2, 70.4, 58.6, 55.1, 29.3, 28.3, 19.1, 18.7, 16.2.

FAB (+) HRMS: Calcd. for $C_{25}Cl_3H_{35}N_2NaO_9$: $(M+Na)^+$: *m/e* 635.13057; Found: *m/e* 635.12828.

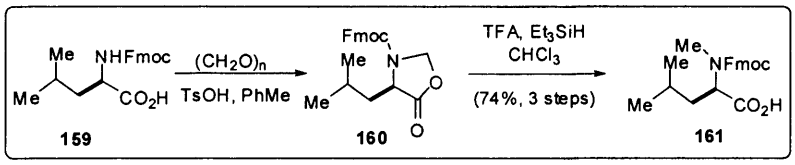
The spectral data for this molecule corresponded with that in the literature.[36]

Acid 159



To D-leucine **158** (10 g, 0.076 mol) in dioxane (75 mL) at 0° C was added 10 % aq. Na_2CO_3 (162 mL, 0.152 mol). A solution of Fmoc-Cl (21.4 g, 0.083 mol) in dioxane (115 mL) was added dropwise over 30 min. The reaction mixture was stirred at 0 °C for 30 min and at rt for 2 h. H_2O (200 mL) was added to the reaction mixture that was extracted with ether (3 x 250 mL). The aqueous layer was acidified to pH 2 with conc. HCl and extracted with EtOAc (3 x 250 mL). The combined organic layers were washed with brine (200 mL), dried ($MgSO_4$) and filtered. The solvent was then removed *in vacuo*. The resulting oil was used for the next step and was not purified any further.

Acid 110



To the crude *N*-Fmoc-D-Leucine **159** (0.076 mol) in dry toluene (330 mL) under N_2 at rt was added paraformaldehyde (2.28 g, 0.076 mol) and TsOH (1.16 g, 6.1 mmol). The mixture was heated at reflux for 1 h and water was removed with a dean-stark apparatus. The reaction mixture was cooled to rt, washed with 10% aq. $NaHCO_3$ (200 mL), dried ($MgSO_4$) and filtered. The solvent was then removed *in vacuo* and compound **160**, which was not characterised any further, was used immediately for the next step as described below.

To crude **160** (25.4 g, 0.0696 mol) in $CHCl_3$ (140 mL) at rt under N_2 was added TFA (134 mL, 1.809 mol) and Et_3SiH (33 mL, 0.209 mol). The reaction mixture was stirred at rt for 2 days and then concentrated in *vacuo*. The residue was co-evaporated from toluene (3 x 100 mL). The crude product crystallised following trituration of the bulk syrup with EtOAc and petrol. Acid **161** was obtained as a white solid (19 g, 74% over 3 steps).

$[\alpha]_D$ + 24.7° (*c* 1.03, CH_2Cl_2).

IR (Neat) 2941 (m), 1753 (s), 1653 (s), 1448 (w), 1327 (w), 1167 (m), 1113 (m), 1038 (w), 806 (w), 762 (m), 739 (m), 650 (w), 606 (w), 542 (w).

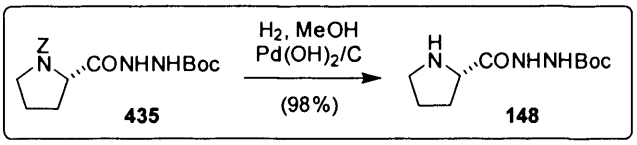
^{1}H-NMR (500 MHz, C_6D_6, 298K) *Major rotamer* δ 7.50 (m, Ph.), 7.40 (m, Ph.), 7.19 (m, Ph.), 5.14 (dd, 1 H, *J* = 11.2, 4.6 Hz, C<u>H</u>CO_2H), 4.42 (m, 2 H, COOC<u>H_2</u>), 3.90 (t, *J* = 6.6 Hz, CO_2CH_2C<u>H</u>), 2.63 (s, 3 H, NC<u>H_3</u>), 1.66 (m, 1 H, C<u>H_2</u>$CHCO_2H$), 1.56 (m, 1 H, C<u>H_2</u>$CHCO_2H$), 1.36 (m, 1 H, C<u>H</u>$(CH_3)_2$), 0.84 (d, *J* = 6.5 Hz, 3 H, $(C$<u>H_3</u>$)_2$), 0.77 (d, *J* = 6.5 Hz, 3 H, $(C$<u>H_3</u>$)_2$); *Minor rotamer* δ 7.50 (m, Ph.), 7.40 (m, Ph.), 7.19 (m, Ph.), 4. 59 (dd, 2 H, *J* = 10.5, 5.3 Hz, COOC<u>H_2</u>), 4.42 (m, 1 H, C<u>H</u>CO_2H), 4.03 (t, *J* = 6.6 Hz, CO_2CH_2C<u>H</u>), 2.76 (s, 3 H, NC<u>H_3</u>), 1.47 (m, 1 H, C<u>H_2</u>$CHCO_2H$), 1.36 (m, 1 H, C<u>H</u>$(CH_3)_2$), 1.26 (m, 1 H, C<u>H_2</u>$CHCO_2H$), 0.66 (d, *J* = 6.5 Hz, 3 H, $(C$<u>H_3</u>$)_2$), 0.59 (d, *J* = 6.5 Hz, 3 H, $(C$<u>H_3</u>$)_2$).

^{13}C-NMR (125 MHz, C_6D_6, 298K) *Major rotamer* : δ 177.5 (NCOO), 157.3 (CO_2H), 144.6 (Ar),144.3 (Ar),141.8 (Ar),128.5 (Ar),125.3 (Ar),125.2 (Ar),120.1 (Ar), 67.7 (COO<u>C</u>H_2), 57.1 (<u>C</u>HCO_2H), 47.7 (CO_2CH_2<u>C</u>H), 37.4 (<u>C</u>H_2CHCO_2H), 30.2 (N<u>C</u>H_3), 25.0 (<u>C</u>H$(CH_3)_2$), 23.2 ($(\underline{C}H_3)_2$), 21.2 ($(\underline{C}H_3)_2$). *Minor rotamer* : δ 177.7 (N<u>C</u>OO), 157.3 (<u>C</u>O_2H), 144.5 (Ar), 144.4 (Ar), 141.8 (Ar),127.3 (Ar),125.0 (Ar), 124.9 (Ar),120.1 (Ar), 67.4 (COO<u>C</u>H_2), 56.8 (<u>C</u>HCO_2H), 47.6 (CO_2CH_2<u>C</u>H), 37.7 (<u>C</u>H_2CHCO_2H, m), 30.7 (N<u>C</u>H_3), 24.8 (<u>C</u>H$(CH_3)_2$), 23.0 ($(\underline{C}H_3)_2$), 21.0 ($(\underline{C}H_3)_2$).

FAB (+) HRMS: Calcd. for $C_{22}H_{25}NaNO_4$: $(M+Na)^+$: *m/e* 390.16812; Found: *m/e* 390.16842.

The spectral data for this molecule corresponded with that in the literature.[36]

Amine 94



To compound **435**[35] (16.7 g, 46 mmol) in dry MeOH (90 mL) at rt was added 10% $Pd(OH)_2$ on carbon (0.490 g, 4.65 mmol). The reaction vessel was sequentially purged with H_2 gas (3 times) before being allowed to stir vigorously under H_2 at rt overnight. The suspension was then filtered through a pad of Celite® and the solvent concentrated *in vacuo*. The resulting white foam (10.28 g) was sufficiently pure for use in the next step and was not purified any further. Therefore, the yield was assumed to be *ca.* 98%.

IR (neat) 3250 (s), 3051 (w), 2974 (s), 2933 (w), 2870 (w), 1743 (s), 1670 (s), 1545 (m), 1394 (w), 1365 (m), 1302 (w), 1248 (s), 1161 (s), 1090 (w), 1045 (w), 874 (w), 762 (w), 627 (w).

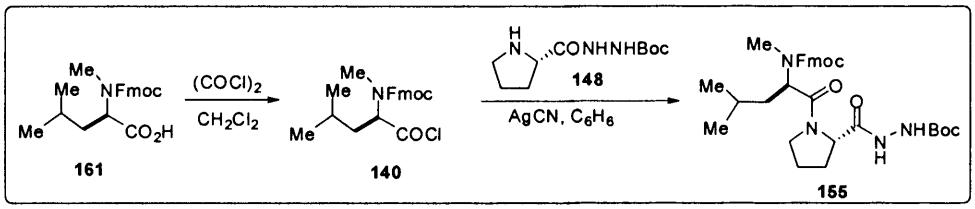
^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 3.82 (dd, *J* = 9.2, 5.2 Hz, 1 H, C<u>H</u>CO), 2.98 (m, 1 H, NC<u>H</u>$_2$), 2.91 (m, 1 H, NC<u>H</u>$_2$), 2.11 (m, 1 H, C<u>H</u>$_2$CHCO), 1.95 (m, 1 H, C<u>H</u>$_2$CHCO), 1.75 (m, 1 H, C<u>H</u>$_2$CH$_2$CHCO), 1.68 (m, 1 H, C<u>H</u>$_2$CH$_2$CHCO), 1.44 (s, 9 H, C(C<u>H</u>$_3$)$_3$).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 174.0 (N<u>C</u>O*O*t-Bu), 155.1 (CH<u>C</u>=ONH), 81.5 (O<u>C</u>(CH$_3$)$_3$), 59.8 (<u>C</u>H), 47.2 (<u>C</u>H$_2$N), 30.5 (<u>C</u>H$_2$CHCO), 28.1 (C(<u>C</u>H$_3$)$_3$), 26.0 (<u>C</u>H$_2$CH$_2$CHCO).

FAB (+) HRMS: Calcd. for $C_{10}H_{10}NaN_3O_3$: $(M+H)^+$: *m/e* 230.15046; Found: *m/e* 230.15177.

The spectral data for this molecule corresponded with that in the literature.[35]

Dipeptide 111



To acid **161** (13.4 g, 0.0366 mol) at rt under N_2 was added dry CH_2Cl_2 (100 mL) followed by $(COCl)_2$ (61 mL, 7.32 mol). The mixture was stirred at rt for 2 h, it was concentrated *in vacuo* and evaporated from C_6H_6 (2 x 50 mL). To the residue was added a solution of the amine **148** (8.4 g, 0.0366 mol) in dry C_6H_6 (120 mL) over 10 min under N_2 at rt. Then AgCN (7.36 g, 0.549 mmol) was added and the reaction mixture was heated at reflux for 30 min. The reaction mixture was cooled to rt and EtOAc (200 mL) was added. The suspension was then filtered through a pad of Celite®, the solvent concentrated *in vacuo*, and the crude residue purified by SiO_2 flash chromatography (gradient elution 2:1 to 1:2 petrol:EtOAc) to give dipeptide **155** as a white foam (19.1 g, 90%).

$[\alpha]_D$ + 3.78° (*c* 0.56, CH_2Cl_2).

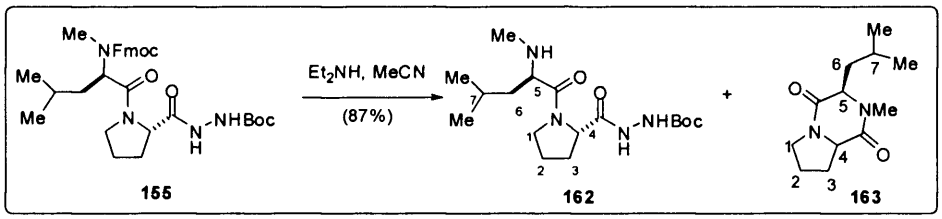
IR (neat) 3288 (br), 2958 (m), 1707 (s), 1697 (s), 1639 (m), 1448 (m), 1396 (w), 1309 (w), 1250 (w), 1159 (m), 1041 (w), 744 (m).

^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 8.63 (br), 8.44 (br), 7.72 (m), 7.66 (m), 7.37 (m), 7.28 (m), 6.52 (m, br), 4.85 (m 1 H), 4.77 (dd, *J* = 11.1, 3.7 Hz, 1 H), 3.51 (m, br), 4.42 (m), 4.31, 4.22 (t), 4.15 (m, br), 4.05 (t) 3.51 (m, br), 2.83 (s, 3 H, $NC\underline{H}_3$), 2.67 (br), 2.45 (m, br), 2.26-1.73 (m, br), 1.59 (m, br), 1.42 (m, br), 1.39 (s, 9 H, $C(C\underline{H}_3)_3$), 0.91 (dd, *J* = 6.6, 2.3 Hz), 0.51 (dd, 3 H, CH-$C\underline{H}_3$), 0.49 (d, 3 H, CH-$C\underline{H}_3$).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 170.9, 170.0, 156.7, 155.5, 154.9, 143.7, 141.2, 127.6, 127.0, 124.9, 124.1, 119.9, 81.1, 67.5, 65.6, 58.7, 58.4, 55.1, 54.4, 47.2, 47.0, 46.0, 37.2, 29.6, 29.4, 28.0, 25.3, 25.0, 24.4, 24.3, 23.1, 22.3.

FAB (+) HRMS: Calcd. for $C_{32}H_{42}N_4NaO_6$: $(M+Na)^+$: *m/e* 601.30019; Found: *m/e* 601.29959.

Dipeptide 162



To dipeptide **155** (19.1 g, 33 mmol) in dry MeCN (240 mL) at rt and under N_2 was added Et_2NH (120 mL, 1.15 mol). The reaction mixture was stirred at rt for 30 min before it was diluted with EtOAc (150 mL) and concentrated *in vacuo*. The crude residue was purified by SiO_2 flash chromatography (gradient elution 1:1 to 0:10 petrol:EtOAc and 1:5 EtOAc:MeOH) to afford a mixture of free amine **162** and diketopiperazine **163** as a white foam (10.22 g, 87%).

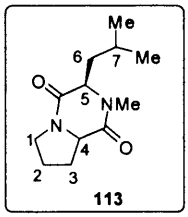
Data for **162**

^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 4.58 (d, *J* = 6.1 Hz, 1 H, H4), 3.77 (td, *J* = 8.9, 6.1 Hz, 1 H, H5), 3.44 (m, 1 H, H1), 3.30 (dd, *J* = 8.8, 4.9 Hz, 1 H, C<u>H</u>NMe), 2.42 (m, 1 H, H1), 2.32 (s, 3 H, NC<u>H</u>$_3$), 2.15 (m, 1 H, H3), 1.98 (m, 2 H, H3, H2), 1.91 (m, 1 H, H2), 1.79 (m, 1 H, H7), 1.42 (s, 9 H, C(C<u>H</u>$_3$)$_3$), 0.91 (dd, *J* = 6.7 Hz, 3 H, CH-C<u>H</u>$_3$), 0.90 (d, *J* = 6.64 Hz, 3 H, CH-C<u>H</u>$_3$).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 175.6 (C=O), 166.0 (C=O), 154.0 (C=O), 81.3 (O<u>C</u>(CH$_3$)$_3$), 60.0 (<u>C</u>HNMe), 58.4 (<u>C</u>HCONHNHBoc), 46.9 (<u>C</u>H$_2$), 42.1 (<u>C</u>H$_2$), 34.8 (N<u>C</u>H$_3$), 28.1 ((<u>C</u>H$_3$)$_3$), 27.1 (C7), 24.8 (<u>C</u>H$_2$CH$_2$N), 24.9 (<u>C</u>H(CH$_3$)$_2$), 23.8 (CH-<u>C</u>H$_3$), 22.0 (CH-<u>C</u>H$_3$).

FAB (+) HRMS: Calcd. for $C_{17}H_{33}N_4O_4$: $(M+H)^+$: *m/e* 225.16029; Found: *m/e* 225.16071.

After purification by SiO_2 flash chromatography diketopiperazine **163** (0.95 g) was isolated:



113

$[\alpha]_D$ - 124.7° (*c* 0.59, CH_2Cl_2)

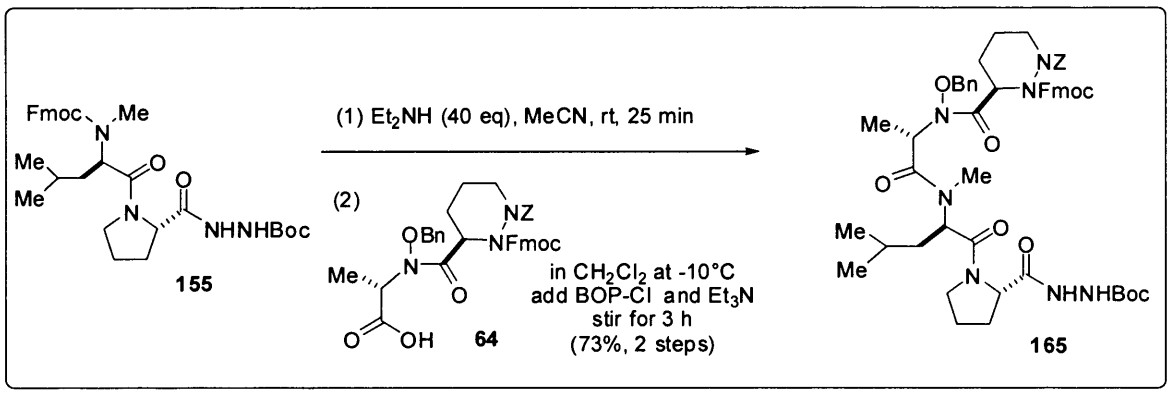
IR (neat film) 2952 (m), 2879 (w), 1872 (s), 1443 (m), 1404 (w), 1304 (w), 1240 (w), 1169 (w).

^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 4.03 (dd, *J* = 9.4, 6.9 Hz, 1 H, H4), 3.77 (dd, *J* = 8.6, 6.3 Hz, 1 H, H5), 3.54 (m, 1 H, H1), 3.46 (m, 1 H, H1), 2.92 (s, 3 H, NC$\underline{H}_3$), 2.35 (m, 1 H, H3), 1.96 (m, 2 H, H3, H2), 1.83 (m, 1 H, H2), 1.75 (m, 1 H, H7), 1.59 (m, 2 H, H6), 1.55 (m, 2 H, H6), 0.91 (d, *J* = 6.6 Hz, 3 H, CH-C$\underline{H}_3$), 0.87 (d, *J* = 6.6 Hz, 3 H, CH-C$\underline{H}_3$).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 167.5 (C=O), 165.9 (C=O), 63.4 (C5), 58.2 (C4), 45.5 (C1), 40.4 (C6), 32.9 (NC$\underline{H}_3$), 29.2 (C3), 24.5 (C7), 22.8 (CH-C$\underline{H}_3$), 22.5 (C2), 22.1 (CH-C$\underline{H}_3$).

FAB (+) HRMS: Calcd. for $C_{12}H_{21}N_2O_2$: $(M+H)^+$: *m/e* 225.16029; Found: *m/e* 225.16071.

Tetrapeptide 165



To dipeptide **155** (2.0 g, 3.46 mmol) in dry MeCN (20 mL) was added at rt under N_2, Et_2NH (10.8 mL, 10.4 mmol). The reaction mixture was stirred at rt under N_2 for 30 min and concentrated *in vacuo*. The crude residue was co-evaporated from benzene (3 x 20 mL) and a

solution of dipeptide **8** (2.3 g, 3.46 mmol) in dry CH_2Cl_2 (18.6 mL) was added at rt under N_2 over 15 min. The reaction mixture was cooled to -10 °C and dry Et_3N (1.06 mL, 7.60 mmol) was added dropwise followed by BOP-Cl (1.06 g, 4.14 mmol). The reactants were allowed to stir at -10 °C for 20 min and at 0 °C for 2.5 h. The reaction mixture was diluted with EtOAc (100 mL) and washed with 0.5 M aq. HCl (2 x 60 mL), 5% aq. $NaHCO_3$ (2 x 60 mL) and brine (60 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The product was purified by SiO_2 flash chromatography (gradient elution 2:1 to 1:2 petrol:EtOAc) to afford tetrapeptide **165** as a white foam (2.55 g, 74%).

$[\alpha]_D$ - 45.0° (*c* 0.74, CH_2Cl_2).

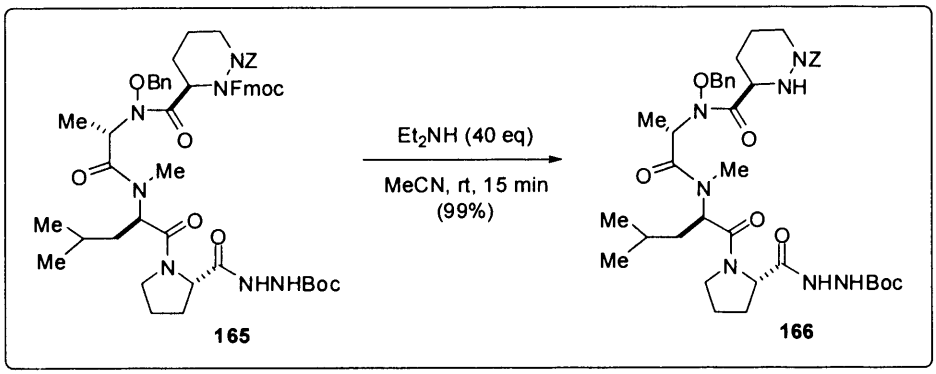
IR (neat) 3304 (br), 2955 (m), 1707 (s), 1649 (s), 1450 (m), 1365 (w), 1296 (w), 1250 (m), 1161 (w), 1090 (w), 1049 (w), 741 (m), 698 (m).

^{1}H-NMR (500 MHz, $CDCl_3$, 298K) 8.65-8.41 (m, br), 7.71-7.01 (m, br), 6.79-6.13 (m, br), 5.54-2.80 (m, br), 2.23 (m, br), 1.80-1.57 (m, br), 1.50-1.11 (m, br), 0.95-0.80 (m, br).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 171.4, 170.6, 170.3, 155.7, 155.4, 155.0, 154.9, 143.7, 143.0, 141.2, 136.3, 136.0, 134.1, 125.4-124.8 (Ar), 119.8, 80.6, 78.6, 68.6, 67.6, 58.6, 53.4, 50.0, 47.3, 46.7, 45.1, 43.8, 37.1, 30.5, 29.6, 28.0, 24.8, 24.5, 23.7, 23.1, 22.8, 22.3, 18.9, 18.5, 14.2.

FAB (+) HRMS: Calcd. for $C_{55}H_{67}N_7NaO_{11}$: $(M+Na)^+$: *m/e* 1024.47960; Found: *m/e* 1024.48548.

Tetrapeptide 166



To tetrapeptide **165** (2.45 g, 2.55 mmol) in dry MeCN (21 mL) under N_2 was added Et_2NH (9.3 mL, 89 mmol) and the reaction mixture was stirred at rt for 25 min and concentrated *in vacuo*. The crude oil was purified by SiO_2 flash chromatography (gradient elution 4:1 to 0:1 petrol:EtOAc) to afford tetrapeptide **166** as a white foam (1.90 g, 99%).

$[\alpha]_D$ + 5.71° (*c* 0.59, CH_2Cl_2).

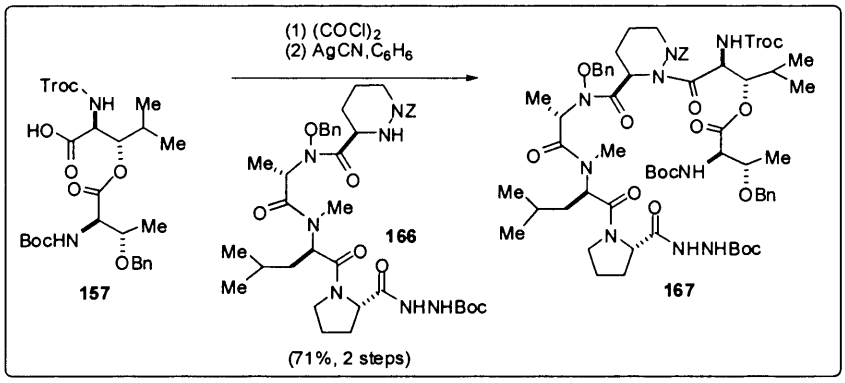
IR (neat) 3292 (br), 2930 (m), 1699 (m), 1645 (s), 1452 (m), 1404 (w), 1367 (w), 1261 (m), 1159 (m), 754 (w), 700 (w).

^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 8.66 (br), 7.35-7.19 (m, br), 6.77 (br), 5.37 (m, br), 5.27 (m, br), 5.18 (d, *J* = 12.3 Hz), 5.07 (d, *J* = 12.3 Hz), 5.11-4.95 (m, br), 4.55 (d, *J* = 8.2 Hz), 4.20 (br), 3.89 (d, *J* = 9.8 Hz), 3.77 (br), 3.42 (br), 3.08 (s, 3 H, $NC\underline{H}_3$), 2.97 (br), 2.21-1.58 (m, br), 1.49 (d, *J* = 6.9 Hz), 1.39 (s, 9 H), 1.22 (s), 0.94 (d, *J* = 7.4 Hz), 0.93 (d, *J* = 6.5 Hz), 0.85 (m, br).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 172.5, 171.6, 170.1, 155.8, 155.5, 136.7, 136.4, 129.0, 128.9, 128.7, 128.4, 128.0, 127.9, 80.8, 80.1, 77.2, 67.2, 59.1, 57.4, 56.6, 54.5, 52.7, 47.6, 44.6, 37.0, 31.7, 30.7, 30.1, 28.1, 26.9, 24.9, 24.5, 23.3, 23.0, 22.4, 13.5.

FAB (+) HRMS: Calcd. for $C_{40}H_{57}N_7NaO_9$: $(M+Na)^+$: *m/e* 802.41153; Found: *m/e* 802.41531.

Depsipeptide 167



To a stirred solution of acid **157** (480 mg, 0.78 mmol) in dry C_6H_6 (2.4 mL) at rt under N_2 was added $(COCl)_2$ (2.4 mL, 27.3 mmol). The reaction mixture was stirred at rt under N_2 for 2.5 h and then concentrated *in vacuo*. The resulting oil was co-evaporated from benzene (3 x 10 mL). To the residue was added a solution of tetrapeptide **166** (610 mg, 0.78 mmol) in dry C_6H_6 (7.2 mL) at rt under N_2. AgCN (167 mg, 1.25 mmol) was then added in one portion. The reaction vessel was fitted with a reflux condenser and immersed for 10 min in an oil bath pre-heated to 80 °C. The reaction mixture was then cooled, diluted with EtOAC (10 mL) and filtered through Celite®, the Celite® was then washed with EtOAc. The filtrate was concentrated *in vacuo* and the product purified by SiO_2 flash chromatography (gradient elution 4:1 to 1:1 petrol:EtOAc) to afford depsipeptide **167** as a white foam (764 mg, 71%).

$[\alpha]_D$ - 57.1° (*c* 0.41, CH_2Cl_2).

IR (neat) 3306 (br), 2876 (w), 2930 (m), 1716 (s), 1643 (s), 1698 (m), 1508 (m), 1452 (m), 1390 (m), 1367 (w), 1240 (m), 1161 (s), 1045 (w), 735(w), 698 (w).

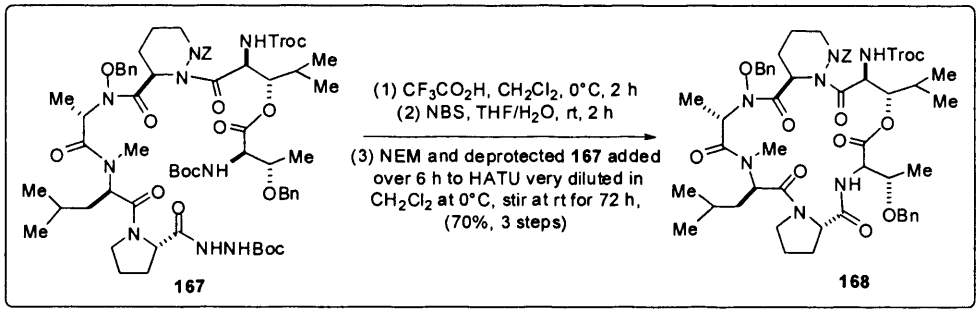
^{1}H NMR (500 MHz, $CDCl_3$, 298K) δ 8.82 (br), 8.54 (br), 8.00 (br), 7.67 (br), 7.49-7.11 (m, br), 6.74 (br), 5.86 (br), 5.59 (br), 5.60 (m, br), 4.47 (m, br), 4.32 (m, br), 4.12 (m, br), 3.73 (m, br), 3.49 (m, br), 3.31 (m, br), 3.07 (m, br), 2.93 (m, br), 2.80 (m, br), 2.60-2.45 (m, br), 2.26 (m, br), 2.10-1.75 (m, br), 1.49-1.25 (m, br), 1.21 (d, *J* = 6.2 Hz), 0.95-0.81 (m, br).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 174.0, 172.4, 171.3, 170.6, 170.4, 169.7, 156.0, 155.5, 155.1, 154.0, 153.3, 137.6, 135.7, 133.5, 129.2, 128.3, 128.6, 128.2, 127.5, 127.4, 126.0,

125.7, 95.3, 81.5, 81.1, 79.8, 79.1, 78.5, 74.4, 70.7, 70.3, 68.6, 68.0, 58.4, 58.1, 57.8, 52.8, 52.4, 51.4, 50.8, 50.6, 48.2, 47.6, 47.1, 45.5, 37.0, 28.6, 28.2, 28.0, 24.8, 24.3, 22.9, 22.7, 22.4, 19.8, 19.6, 17.9, 17.1, 16.3, 16.1, 15.9, 13.9.

FAB (+) HRMS: Calcd. for $C_{65}Cl_3H_{90}N_9NaO_{17}$: $(M+Na)^+$: *m/e* 1396.54176; Found: *m/e* 1396.54502.

Cyclodepsipeptide 168



To depsipeptide **167** (1.19 g, 0.865 mmol) in dry CH_2Cl_2 (13.4 mL) at 0 °C under N_2 was added in one portion CF_3CO_2H (13.4 mL, 0.17 mol). The reaction mixture was stirred for 2 h at 0 °C, concentrated *in vacuo* and co-evaporated from toluene (2 x 10 mL) to remove the excess CF_3CO_2H. To the residue in THF (9.7 mL) and H_2O (9.7 mL) was added NBS (0.31 g, 1.7 mmol) portionwise over 10 min. The reaction mixture was stirred at rt for 2 h, diluted with EtOAc (50mL) and washed with brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* affording a white foam. To a suspension of HATU (3.28 g, 8.65 mmol) in dry CH_2Cl_2 (1 L) at 0 °C and under N_2 was added dropwise over 5 h, a solution of the above crude product and *N*-ethylmorpholine (1.48 mL, 11.6 mmol) in dry CH_2Cl_2 (1 L). The reaction mixture was stirred at rt for 60 h. The reaction mixture was concentrated *in vacuo* and the yellow residue dissolved in EtOAc (300 mL), washed with 1 M aq. HCl (2 x 70 mL), 5% aq. $NaHCO_3$ (2 x 70 mL) and brine (70 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The product was purified by SiO_2 flash chromatography (gradient elution 4:1 to 2:1 petrol:EtOAc) to afford cyclodepsipeptide **168** as a white foam (698 mg, 70% over 3 steps).

$[\alpha]_D$ + 3.90° (*c* 0.59, CH_2Cl_2).

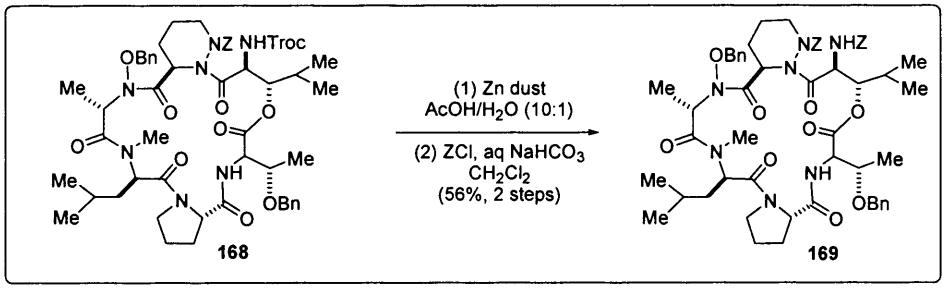
IR (neat) 3290 (br), 2876 (w), 1739 (s), 1676 (s), 1641 (s), 1508 (m), 1452 (w), 1391 (m), 1234 (m), 1196 (w), 1153 (w), 1090 (w), 1040 (w), 999 (w), 746 (m), 700 (m).

^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 7.44-7.17 (m, br), 5.86-5.39 (m, br), 5.24-4.49 (m, br), 4.21-4.01 (m, br), 3.91 (m, br), 3.84 (m, br), 3.78 (m, br), 3.42 (m, br), 3.44 (m, br), 3.26, 3.21 (m, br), 2.94 (m, br), 2.83 (m, br), 2.07-1.65 (m, br), 1.56 (m, br), 1.50-1.40 (m, br), 1.23 (br), 1.17 (d, *J* = 6.4 Hz), 1.15 (d, *J* = 6.4 Hz), 0.98-0.73 (m, br).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 173.1, 172.3, 171.2, 170.1, 169.5, 168.7, 165.7, 157.8, 155.8, 153.9, 153.1, 137.8, 135.3, 134.0, 129.5, 128.9, 128.5, 128.2, 127.9, 127.5, 95.1, 79.5, 74.9, 70.7, 69.0, 60.4, 59.0, 58.7, 57.2, 55.9, 55.6, 53.5, 53.0, 51.1, 49.6, 48.2, 47.8, 46.9, 45.7, 37.7, 37.4, 30.3, 29.7, 29.6, 28.4, 28.0, 27.7, 26.4, 24.9, 24.7, 23.2, 22.9, 22.7, 22.2, 19.5, 17.1, 15.8, 15.5, 14.9, 13.8.

FAB (+) HRMS: Calcd. for $C_{55}Cl_3H_{70}N_7NaO_{13}$: $(M+Na)^+$: *m/e* 1164.39946; Found: *m/e* 1164.39772.

Cyclodepsipeptide 169



To cyclodepsipeptide **168** (337 mg, 0.296 mmol) in a solution of 10 :1 AcOH:H_2O (7.7 mL) at rt was added Zn dust (387 mg, 5.90 mmol). The reaction mixture was left to stir at rt for 1 h and was filtered through Celite®. The Celite® pad was washed with THF (50 mL) and the filtrate was concentrated *in vacuo* and the residue co-evaporated from toluene (2 x 6 mL). To the resulting residue was added dropwise and simultaneously, over 10 min, a solution of Z-Cl (0.13 mL, 0.888 mmol) in CH_2Cl_2 (1.55 mL) and 10% aq. $NaHCO_3$ (1.55 mL). The reaction mixture was diluted with EtOAc (20 mL), washed with brine (10 mL), dried over $MgSO_4$, filtered

and concentrated *in vacuo*. The product was purified by SiO_2 flash chromatography (gradient elution 4:1 to 2:1 petrol:EtOAc) to afford **169** as a white foam (184 mg, 56% over 2 steps).

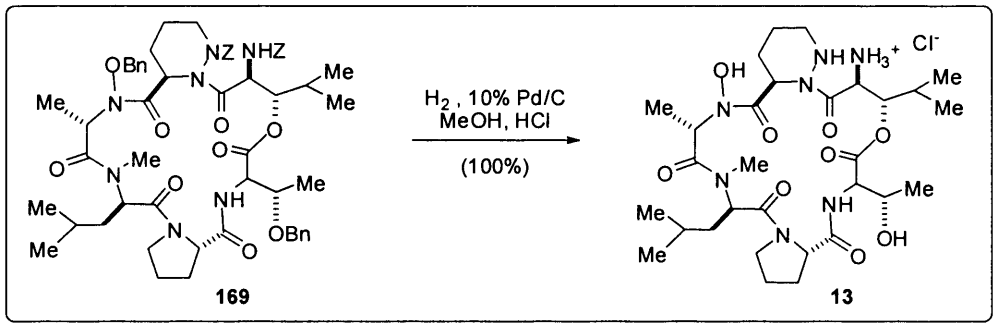
IR (neat) 3302 (m), 2959 (m), 1728 (s), 1676 (s), 1634 (s), 1506 (m), 1452 (w), 1394 (m), 1257 (m), 1236 (m), 1194 (w), 1151 (w), 1035 (w), 1001 (w), 741 (m), 700 (m).

^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 7.45-7.09 (m, br), 6.73 (m, br), 5.76-5.49 (m, br), 5.42 (m, br), 5.27-5.81 (m, br), 4.70 (m, br), 4.63-4.47 (m, br), 4.15 (m, br), 4.07 (m, br), 3.91 (m, br), 3.78 (m, br), 3.69 (m, br), 3.43 (m, br), 3.25 (m, br), 3.23 (m, br), 2.94 (m, br), 2.81 (m, br), 2.01-1.40 (m, br), 1.23 (s), 1.16 (m), 0.96-0.70 (m, br).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 173.0, 171.1, 170.4, 170.1, 169.8, 169.5, 168.7, 165.8, 157.8, 155.4, 154.8, 137.8, 136.2, 135.8, 135.4, 134.0, 129.6, 128.9, 128.6, 128.5, 128.3, 128.2, 128.1, 128.0, 127.8, 127.5, 127.4, 79.1, 77.9, 75.3, 74.6, 77.2, 70.8, 70.5, 68.9, 68.7, 67.0, 59.0, 57.1, 55.6, 52.8, 52.4, 51.1, 50.8, 49.3, 48.2, 47.8, 46.8, 45.7, 45.1, 37.6, 37.3, 30.3, 29.8, 28.4, 27.9, 26.4, 25.1, 24.9, 24.6, 23.2, 23.0, 22.7, 22.1, 19.6, 17.2, 15.6, 15.0, 13.6.

FAB (+) HRMS: Calcd. for $C_{60}H_{75}N_7NaO_{13}$: $(M+Na)^+$: *m/e* 1124.53203; Found: *m/e* 1124.52750.

Cyclodepsipeptide 13

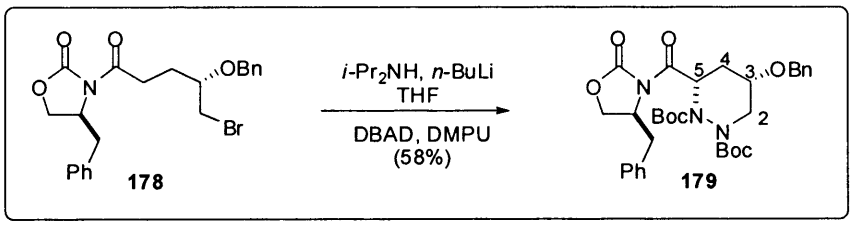

NZ NHZ
OBn
Me
Me
Me
Me
Me
Me
NH
OBn
Me
Me
Me
O
O
O

^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 6.17 (m), 6.06 (br), 5.80, 5.64, 5.58, 5.49 (m, br), 5.08 (s), 5.03 (br), 4.72 (m, br), 4.65 (s, br), 4.59 (m, br), 4.56-4.47 (m, br), 4.43 (m, br), 4.34 (m, br), 4.10-3.38 (m, br), 3.22 (m, br),3.13 (m, br),3.02 (m, br), 2.97 (m, br), 2.93 (s, 3 H, NCH_3), 2.31-1.44 (m, br), 1.36 (d), 1.33 (m, br), 1.21 (d), 1.17 (m, br), 1.07 (m, br), 0.95 (s, br).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 174.9, 174.4, 173.1, 172.9, 172.3, 171.7, 171.4, 171.2, 170.9, 170.1, 169.8, 168.4, 168.1, 156.7, 79.4, 79.0, 75.4, 70.6, 70.1, 69.4, 68.7, 67.8, 66.5, 63.2, 62.1, 61.6, 61.3, 58.8, 58.3, 56.9, 56.5, 55.1, 54.5, 54.1, 53.2, 52.5, 51.8, 50.4, 49.8, 46.3, 38.3, 31.5, 31.0, 30.8, 29.6, 29.4, 28.4, 27.9, 26.5, 26.0, 25.9, 25.8, 25.7, 23.4, 23.3, 23.1, 22.9, 22.4, 22.1, 21.5, 21.1, 20.4, 20.2, 20.1, 19.8, 19.4, 18.2, 16.1, 15.1, 14.9, 14.5.

The NMR analysis showed that the salt is not pure.

Oxazolidinone 179



To a stirred solution of diisopropylamine (0.93 mL, 6.65 mmol) in THF (5.7 mL) at -78 °C was added dropwise *n*-BuLi (2.5 M in hexanes, 2.7 mL, 6.65 mol). The reaction mixture was stirred at -78 °C for 35 min. A solution of the bromide **178**[38] (2.7 g, 6.04 mmol) in THF (6 mL) was added dropwise to the mixture. The mixture was stirred at -78 °C for 75 min and a solution of DBAD (1.67 g, 7.26 mmol) in CH_2Cl_2 (7 mL) was added. After 1h 40 min at -78 °C, DMPU (11.7 mL, 96.8 mmol) was added dropwise and the mixture was maintained at -78 °C for 5 min, then allowed to warm to rt and stirred at rt for 50 min. The mixture was added to a flask containing EtO_2 (170 mL) and sat. aq. KH_2PO_4 (100 mL). The organic layer was washed with water (100 mL), brine (100 mL), dried ($MgSO_4$) and filtered. The solvent was then removed *in vacuo* and the crude residue was purified by SiO_2 flash chromatography (graduent elution 8:1 to

5:1 petrol:EtOAc) and recrystallised with petrol and ether to afford compound **179** as a white solid (2.10 g, 58 %).

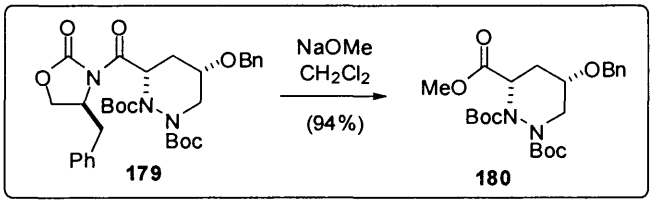
$[\alpha]_D$ + 50.7 (*c* 0.49, CH_2Cl_2).

^{1}H-NMR (400 MHz, DMSO, 353K) δ 7.26 (m, Ar), 5.73 (m br, 1 H, H5), 4.56 (d, *J* = 11.9 Hz, 1 H, OC$\underline{H}_2$Ar), 4.51 (br, 1 H, C$\underline{H}$NH), 4.47 (d, *J* = 11.9 Hz, 1 H, OC$\underline{H}_2$Ar), 4.22 (br, 1 H, H2), 4.14 (m, 2 H, C$\underline{H}_2$O), 3.72 (m, br, 1 H, H3), 3.14 (m br, 1 H, H2), 3.09 (m, br, 1 H, C$\underline{H}_2$Ar), 2.92 (m, br, 1 H, C$\underline{H}_2$Ar), 2.13 (ddd, *J* = 3.3, 6.9, 14.1 Hz 1 H, H4), 1.97 (m, br, 1 H, H4), 1.46 (s, CH_3), 1.48 (s, CH_3).

^{13}C-NMR (125 MHz, C_6H_6, 353K) δ 168.8, 167.6 (br), 153.3 (O=$\underline{C}$(O*t*Bu)), 152.5, 138.1, 135.2, 128.8, 128.0, 127.5, 126.9, 126.3, 80.6, 78.9, 69.2, 69.1, 66.3, 54.8, 52.5 (br), 36.3, 29.6, 27.4 (C($\underline{C}H_3$)$_3$), 27.5 (C($\underline{C}H_3$)$_3$).

The spectral data for this molecule corresponded with that in literature.[38]

Ester 180



To a solution of **179** (11.8 g, 19.8 mmol) in CH_2Cl_2 (120 mL) was added a solution of NaOMe (0.4 M, 55 mL, 21.8 mmol) at - 30 °C. The reaction mixture was stirred at -30 °C for 15 min and then was neutralised to pH 6 with 10% aq. KH_2PO_4. The mixture was then extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried ($MgSO_4$) and filtered. The solvent was then removed *in vacuo* and the crude residue was purified by SiO_2 flash chromatography with 4:1 petrol:EtOAc as eluent to afford the title compound **180** as a yellow oil (8.40 g, 94 %).

$[\alpha]_D$ - 8.45° (*c* 0.72, CH_2Cl_2).

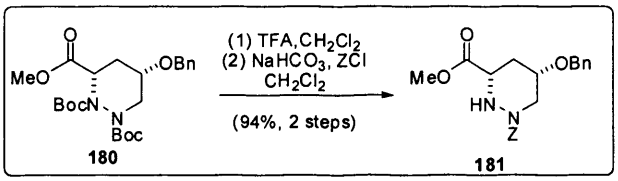
IR (neat) 2978 (m), 2932 (w), 1763 (m), 1732 (s), 1697 (s), 1450 (w), 1416 (s), 1392 (s), 1365 (s), 1342 (m), 1296 (m), 1250 (m), 1171 (s), 1132 (m), 1094 (s), 858 (w), 752 (w), 735 (w).

^{1}H-NMR (400 MHz, DMSO, 353K) δ 7.28 (m, Ar), 4.78 (dd, *J* = 2.8, 6.9 Hz, 1 H, BocNC<u>H</u>COOMe), 4.52 (d, *J* = 11.6 Hz, 1 H, OC<u>H</u>$_2$Ar), 4.43 (d, *J* = 11.6 Hz, 1 H, OC<u>H</u>$_2$Ar), 4.22 (d br, *J* = 13.0 Hz, C<u>H</u>$_2$NBoc), 3.68 (m, br, 1 H, C<u>H</u>OBn), 3.48 (s, 3 H, OC<u>H</u>$_3$), 3.0 (m, 1 H, C<u>H</u>$_2$NBoc), 2.32 (d, br, *J* = 2.3 Hz, 1 H, CH-C<u>H</u>$_2$-CH), 1.95 (ddd, *J* = 2.9, 6.9, 14.1 Hz 1 H, CH-C<u>H</u>$_2$-CH), 1.43 (s, 9 H, C(C<u>H</u>$_3$)$_3$), 1.42 (s, 9 H, C(C<u>H</u>$_3$)$_3$).

^{13}C-NMR (125 MHz, C_6H_6, 333K) δ 169.4 (MeO<u>C</u>=O), 153.2 (C=O), 138.1, 127.4, 126.6, 80.6 , 78.8 (<u>C</u>(CH$_3$)$_3$), 78.6 (<u>C</u>(CH$_3$)$_3$), 68.9 (O<u>C</u>H$_2$Ar), 68.6 (<u>C</u>HOBn), 52.1 (br, <u>C</u>HNBoc), 50.8 (O<u>C</u>H$_3$), 44.6 (br, <u>C</u>H$_2$NBoc), 28.9 (CH-<u>C</u>H$_2$-CH), 27.5 (C(<u>C</u>H$_3$)$_3$), 27.4 (C(<u>C</u>H$_3$)$_3$).

FAB (+) HRMS: Calcd. for $C_{23}H_{38}N_2O_4$: $(M+H)^+$: *m/e* 451.24441; Found: *m/e* 451.24565.

Ester 181



To a solution of **180** (8.40 g, 18.6 mmol) in CH_2Cl_2 (50 mL) was added TFA (13.8 mL, 186 mmol). The reaction mixture was stirred at rt for 2 h and evaporated *in vacuo*. The oil was co-evaporated from CH_2Cl_2 and used directly for the next step.

To a solution of crude TFA salt (18.6 mmol) in CH_2Cl_2 (122 mL) was added at 0°C, 10% aq. $NaHCO_3$ (18.6 mL). Then a solution of ZCl in CH_2Cl_2 (1 M, 18.6 mL, 18.6 mmol) was added dropwise *via* pipette over 15 min. After stirring 20 min at rt, the layers were separated and the aqueous layer extracted with EtOAc (3 x 100 mL). The combined organic layers were dried ($MgSO_4$) and filtered. The solvent was then removed *in vacuo* and the crude residue was purified by SiO_2 flash chromatography with 2:1 petrol:EtOAc as eluent to afford compound **181** as a yellow oil (6.8 g, 94 % over 2 steps).

$[\alpha]_D$ + 20.2° (*c* 0.28, CH_2Cl_2).

IR (neat) 3283 (w), 3032 (w), 2951 (m), 2870 (m), 1742 (s), 1705 (s), 1605 (w), 1497 (w), 1448 (m), 1410 (m), 1350 (m), 1269 (m), 1111 (m), 1169 (s), 1092 (m), 1028 (w), 744 (m), 700 (m).

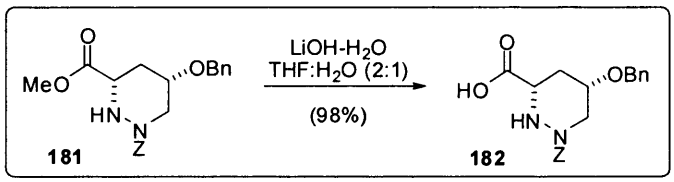
^{1}H-NMR (500 MHz, C_6H_6, 333K) δ 7.31 (d, *J* = 7.3 Hz , Ar), 7.31 (m, Ar), 5.18 (d, *J* = 12.3 Hz, 1 H, COOC$\underline{H}_2$Ar), 5.09 (d, *J* = 12.3 Hz, 1 H, COOC$\underline{H}_2$Ar), 4.12 (d, *J* = 12.3 Hz, 1 H, OC$\underline{H}_2$Ar), 4.06 (d, *J* = 12.3 Hz, 1 H, OC$\underline{H}_2$Ar), 3.73 (m, br, 1 H, HNC$\underline{H}$COOH), 3.38 (s, 3 H, OC$\underline{H}_3$), 3.10 (m, br, 2 H, C$\underline{H}_2$NZ), 3.14 (m, 1 H, C$\underline{H}$OBn), 2.49 (d, br, *J* = 18.0 Hz, 1 H, CH-C$\underline{H}_2$-CH), 2.09 (ddd, *J* = 2.2, 4.6, 18.8 Hz 1 H, CH-C$\underline{H}_2$-CH).

^{13}C-NMR (125 MHz, C_6H_6, 333K) δ 165.0 (MeO$\underline{C}$=O), 154.5 (C=O), 138.3 (Ar), 136.7 (Ar), 128.7-127.6 (Ar), 70.2 (O$\underline{C}H_2$Ar), 68.3 ($\underline{C}$HOBn), 65.4 (COO$\underline{C}H_2$Ar), 51.7 (O$\underline{C}H_3$), 51.6 (HN$\underline{C}$HCOOH), 44.5 ($\underline{C}H_2$NZ), 38.4 (CH-$\underline{C}H_2$-CH).

FAB (+) HRMS: Calcd. for $C_{21}H_{24}N_2NaO_5$: $(M+Na)^+$: *m/e* 407.15828; Found: *m/e* 407.15878.

The spectral data for this molecule corresponded with that in literature.[38]

Acid 182



To a mixture of ester **181** (3.75 g, 9.7 mmol) in THF/H_2O (2:1, 74 mL:37 mL) at 0 °C was added LiOH-H_2O (0.409 g, 9.7 mmol). The resulting mixture was stirred 15 min at 0 °C. 10% aq. HCl was added until pH 2 was attained and the mixture was extracted with EtOAc (3 x 80 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and filtered. The solvent was then removed *in vacuo* and the resulting oil (3.54 g) was sufficiently pure for use in

the next step and was not purified any further. Therefore, the yield of the formation of **182** was assumed to be *ca.* 98%.

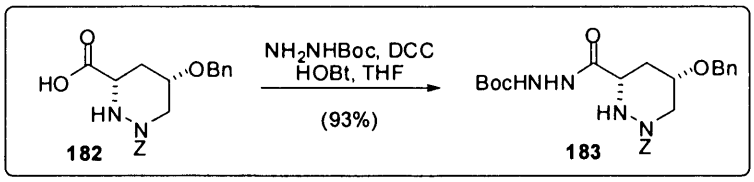
IR (neat) 3210 (br), 3032 (w), 2920 (br), 1703 (s), 1497 (w), 1452 (w), 1410 (m), 1354 (w), 1257 (m), 1178 (m), 1122 (m), 1092 (m), 1153 (w), 742 (m), 700 (m).

^{1}H-NMR (400 MHz, C_6H_6, 333K) δ 7.22-7.03 (m, 10 H, Ar), 6.76 (br, 2 H, NH, OH), 5.05 (d, *J* = 12.5 Hz, 1 H, COOCH_2Ar), 5.00 (d, *J* = 12.5 Hz, 1 H, COOCH_2Ar), 4.37 (d, *J* = 12.1 Hz, 1 H, OCH_2Ar), 4.20 (d, *J* = 12.1 Hz, 1 H, OCH_2Ar), 3.44 (dd, *J* = 13.1, 6.2 Hz, 1 H, HNCHCOOH), 3.23 (t, *J* = 5.7 Hz, 2 H, CH_2NZ), 3.14 (m, 1 H, CHOBn), 2.17 (m, 1 H, CH-CH_2-CH), 1.67 (m, 1 H, CH-CH_2-CH).

^{13}C-NMR (125 MHz, C_6H_6, 333K) δ 172.7 (C=O), 157.1 (C=O), 138.4 (Ar), 136.6 (Ar), 128.7-127.6 (Ar), 70.5 (OCH_2Ar), 70.3 (CHOBn), 68.3 (COOCH_2Ar), 55.7 (HNCHCOOH), 48.8 (CH_2NZ), 30.8 (CH-CH_2-CH).

FAB (+) HRMS: Calcd. for $C_{20}H_{22}N_2NaO_5$: $(M+H)^+$: *m/e* 371.16069; Found: *m/e* 371.16179.

Compound 183



To acid **182** (9.7 mmol) in dry THF (55 mL), was added at 0 °C under N_2, HOBt (1.42 g, 10.5 mmol), DCC (2.17 g, 10.5 mmol) and $BocNHNH_2$ (1.39 g, 10.5 mmol). The reaction mixture was stirred at 0 °C for 30 min and at rt overnight. The suspension was then filtered through a pad of Celite®, the filtrate was washed with 1 M aq. HCl (50 mL), 5% aq. $NaHCO_3$ (50 mL) and brine (50 mL). The organic layer was dried on $MgSO_4$ and concentrated *in vacuo*, the crude residue was purified by SiO_2 flash chromatography (gradient elution 2:1 to 1:2 petrol:EtOAc) to give **183** as a white foam (4.3 g, 93%).

$[\alpha]_D$ - 40.8° (*c* 0.51, CH_2Cl_2).

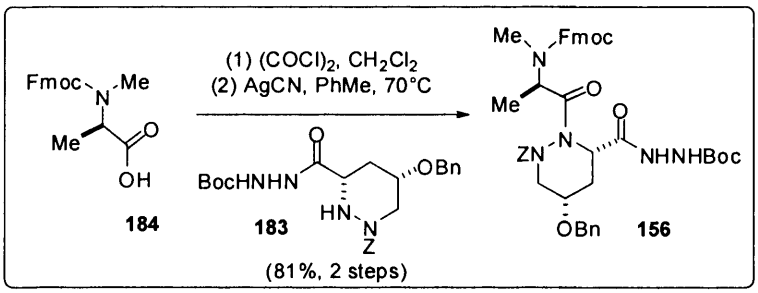
IR (neat) 3277 (br), 2977 (w), 2930 (w), 1695 (s), 1499 (w), 1454 (w), 1367 (w), 1344 (m), 1163 (s), 1124 (m), 1091 (w), 1026 (w), 737 (w), 698 (w).

^{1}H-NMR (400 MHz, C_6H_6, 333K) δ 9.47 (s, 1 H, CONH) 7.25-7.06 (m, 10 H, Ar), 6.76 (br, 2 H, NH, OH), 5.11 (d, *J* = 12.5 Hz, 1 H, $COOCH_2Ar$), 5.07 (d, *J* = 12.5 Hz, 1 H, $COOCH_2Ar$), 4.42 (d, *J* = 12.1 Hz, 1 H, OCH_2Ar), 4.27 (d, *J* = 12.1 Hz, 1 H, OCH_2Ar), 3.56 (dd, *J* = 13.2, 6.0 Hz, 1 H, CH_2NZ), 3.43 (t, *J* = 5.7 Hz, 1 H, HNCHCOOH), 3.32 (dd, *J* = 13.2, 1.6 Hz, 1 H, CH_2NZ), 3.28 (m, 1 H, CHOBn), 2.30 (m, 1 H, CH-CH_2-CH), 1.79 (m, 1 H, CH-CH_2-CH), 1.36 (s, 9 H, $C(CH_3)_3$).

^{13}C-NMR (125 MHz, C_6H_6, 333K) δ 170.5 (C=O), 156.7 (C=O), 155.8 (C=O), 139.3 (Ar), 137.1 (Ar), 128.7-127.5 (Ar), 80.6 ($C(CH_3)$, 70.4 (OCH_2Ar), 70.2 (CHOBn), 67.9 ($COOCH_2Ar$), 56.0 (HNCHCOOH), 49.0 (CH_2NZ), 30.3 (CH-CH_2-CH), 28.3 ($C(CH_3)$).

FAB (+) HRMS: Calcd. for $C_{25}H_{33}N_4O_6$: $(M+H)^+$: *m/e* 485.24000; Found: *m/e* 485.23909.

Dipeptide 156



To acid **184** (2.0 g, 6.34 mmol, dried from C_6H_6) at rt under N_2 was added dry CH_2Cl_2 (15 mL) followed by $(COCl)_2$ (11.06 mL, 127 mmol). The mixture was stirred at rt for 2 h, concentrated *in vacuo* and dried from C_6H_6. To the residue was added a solution of the amine **183** (2.9 g, 6.02 mmol, dried from C_6H_6) in C_6H_6 (20 mL) at rt under N_2. Then AgCN (1.27 g, 9.51 mmol) was added and the reaction mixture was heated at reflux for 40 min. The reaction mixture was cooled to rt and EtOAc was added (30 mL). The suspension was then filtered through a pad of Celite®, the solvent concentrated *in vacuo*, and the crude residue was purified by SiO_2 flash chromatography (gradient elution 3:1 to 1:1 petrol:EtOAc) to give **156** as a white foam (3.95 g, 81%, 2 steps).

$[\alpha]_D$ + 3.97° (*c* 0.57, CH_2Cl_2).

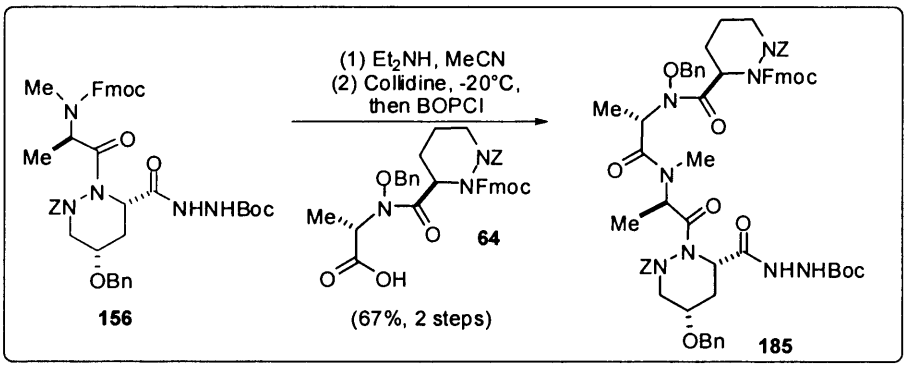
IR (neat) 3284 (br), 2977 (w), 1703 (s), 1450 (m), 1403 (m), 1365 (w), 1310 (w), 1241 (m), 1159 (m), 1120 (w), 1153 (w), 741 (m), 698 (m).

^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 9.98 (m, br), 7.75-7.65 (m, br), 7.42-7.04 (m, br), 6.12 (m, br), 5.34-4.68 (m, br), 4.50 (d, *J* = 12.3 Hz), 4.33 (d, *J* = 12.3 Hz), 4.44-4.08 (m, br), 4.57 (m, br), 3.37 (m, br), 3.16 (d), 2.93 (br), 2.84-2.50 (m, br), 2.32 (br), 1.87 (br), 1.72 (br), 1.45 (s) 1.41 (s), 1.30 (m, br), 0.86 (m, br).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 174.0, 168.8, 157.8, 155.8, 154.5, 143.7, 141.1, 137.8, 134.8, 128.6, 128.5, 128.3, 128.2, 127.9, 127.6, 127.4, 127.1, 127.0, 125.5, 124.9, 124.4, 124.2, 119.8, 80.8, 69.7, 69.0, 67.7, 67.5, 66.4 52.1, 51.6, 50.9, 50.0, 47.0, 29.6, 29.1, 28.0, 27.2, 27.0, 14.9, 14.1.

FAB (+) HRMS: Calcd. for $C_{44}H_{49}N_5NaO_9$: $(M+Na)^+$: *m/e* 814.34278; Found: *m/e* 814.34649.

Tetrapeptide 185



To dipeptide **156** (2.0 g, 2.52 mmol) in dry MeCN (20 mL) was added at rt under N_2, Et_2NH (9.2 mL, 88.4 mmol). The reaction mixture was stirred at rt under N_2 for 30 min and concentrated *in vacuo*. The crude residue was co-evaporated from benzene. Dipeptide **64** (1.6 g, 2.41 mmol) in dry CH_2Cl_2 (4.2 mL) at rt under N_2 was cooled at -10 °C and dry collidine (0.62 mL, 5.55 mmol) followed by BOP-Cl (0.737 g, 3.03 mmol) were added. The reaction mixture was stirred at -10 °C for 20 min and a solution of the deprotected amine in dry CH_2Cl_2 (5.0 mL) was added at -10 °C. The reactants were allowed to stir at -10 °C for 20 min and at 0 °C for 2.5 h. The reaction mixture was diluted with EtOAc (80 mL), washed with 0.5 M aq. HCl (2 x 40 mL), 5% aq. $NaHCO_3$ (2 x 40 mL) and brine (40 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was purified by SiO_2 flash chromatography (gradient elution 3:1 to 1:2 petrol:EtOAc) to afford tetrapeptide **185** as a white foam (2.07 g, 67%, 2 steps).

$[\alpha]_D$ - 25.8° (*c* 0.69, CH_2Cl_2).

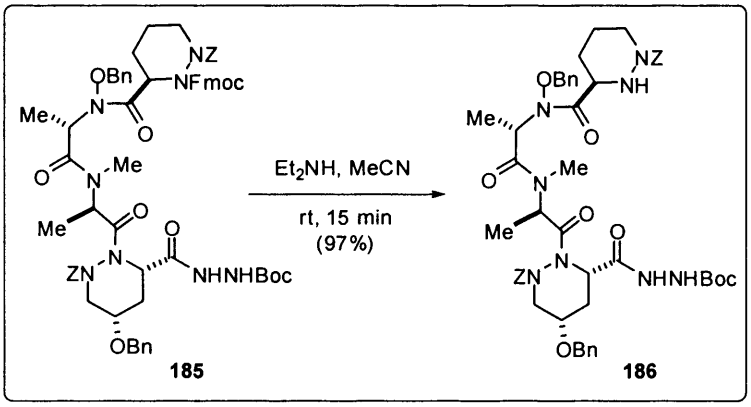
IR (neat) 3290 (br), 2974 (m), 1716 (S), 1666 (s), 1499 (m), 1456 (m), 1392 (m), 1242 (s), 1161 (s), 1124 (w), 1078 (w), 999 (w), 735 (m), 700 (m).

^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 9.84 (br), 9.62 (br), 7.76-7.10 (m, br), 6.73 (m, br), 5.60-4.70 (m, br), 4.58-3.86 (m, br), 3.70-2.59 (m, br), 2.28 (m, br), 2.12 (m, br), 2.02 (m, br), 1.88-1.68 (m, br), 1.42 (s), 1.39-1.32 (m, br), 1.24 (m, br).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 172.3, 169.8, 168.7, 164.0, 158.7, 155.7, 154.5, 154.1, 143.7, 143.1, 141.2, 137.9,136.4, 135.9, 135.2, 134.7, 128.4, 128.2, 127.7, 127.4, 127.2, 127.0, 125.0, 119.9, 80.9, 78.5, 70.5, 69.7, 68.5, 67.4, 57.5, 57.0, 56.0, 52.8, 52.1, 49.7, 46.7, 45.2, 43.9, 35.0, 32.1, 29.8, 28.0, 26.9, 24.0, 23.7, 18.8, 18.4, 15.6, 13.9.

FAB (+) HRMS: Calcd. for $C_{67}H_{74}N_8NaO_{14}$: $(M+Na)^+$: *m/e* 1237.52219; Found: *m/e* 1237.52395.

Tetrapeptide 186



To tetrapeptide **185** (1.90 g, 1.56 mmol) in dry MeCN (15 mL) under N_2 was added Et_2NH (5.7 mL, 54.7 mmol) and the reaction mixture was stirred at rt for 25 min and concentrated *in vacuo*. The crude residue was purified by SiO_2 flash chromatography (gradient elution 4:1 to 0:1 petrol:EtOAc) to afford tetrapeptide **186** as a white foam (1.5 g, 97%).

$[\alpha]_D$ - 35.3° (*c* 0.43, CH_2Cl_2).

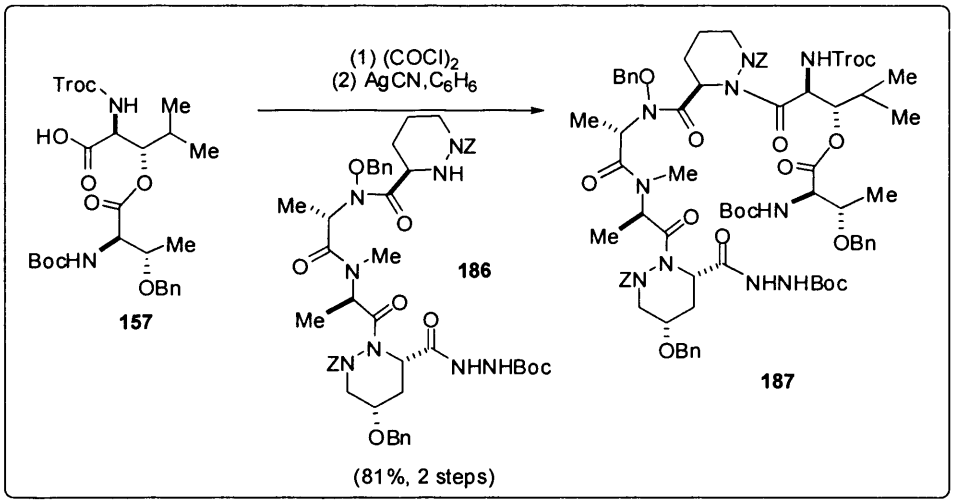
IR (neat) 3284 (br), 2935 (w), 1701 (s), 1653 (s), 1452 (m), 1406 (m), 1364 (w), 1310 (w), 1259 (m), 1161 (m), 1122 (w), 1083 (w), 744 (m), 700 (m).

^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 9.80 (br), 9.61 (br), 8.58 (br), 7.36-7.15 (m, br), 6.18 (br), 6.0 (br), 6.73 (m, br), 5.45-4.85 (m, br), 4.50-3.80 (m, br), 3.70-2.59 (m, br), 2.30-1.67 (m, br), 1.52-1.20 (m, br).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 174.0, 173.2, 172.6, 169.7, 169.2, 168.8, 158.7, 155.7, 155.0, 154.6, 137.9, 137.6, 136.5, 136.2, 135.2, 134.2, 133.5, 129.4, 129.0, 128.6, 128.4, 128.2, 127.9, 127.4, 127.2, 80.9, 78.7, 69.7, 67.2, 56.5, 52.5, 51.2, 46.8, 45.0, 31.6, 30.0, 29.5, 28.0, 26.8, 23.0, 15.8, 14.5, 13.9.

FAB (+) HRMS: Calcd. for $C_{52}H_{64}N_8NaO_{12}$: $(M+Na)^+$: *m/e* 1015.45412; Found: *m/e* 1015.46087.

Depsipeptide 131



To acid **157** (303 mg, 0.49 mmol) in dry C_6H_6 (1.5 mL) at rt under N_2 was added $(COCl)_2$ (1.5 mL, 17.2 mmol). The reaction mixture was stirred at rt under N_2 for 2.5 h and concentrated *in vacuo*. The resulting oil was co-evaporated from benzene. To the residue was added a solution of tetrapeptide **186** (600 mg, 0.49 mmol) in dry C_6H_6 (4.6 mL) at rt under N_2. AgCN (106 mg, 0.79 mmol) was then added in one portion. The reaction vessel was fitted with a reflux condenser and immersed for 10 min in an oil bath pre-heated to 80°C. The reaction mixture was then cooled, diluted with EtOAC and filtered through Celite®, the Celite® was then washed with EtOAc. The filtrate was concentrated *in vacuo* and the product purified by SiO_2 flash chromatography (gradient elution 4:1 to 1:3 petrol:EtOAc) to afford depsipeptide **187** in the form of two isomers **187a** (339 mg, 43%) and **187b** (375 mg, 48%).

$[\alpha]_D$ - 42.5° (*c* 0.59, CH_2Cl_2)

$[\alpha]_D$ - 12.3° (*c* 0.60, CH_2Cl_2)

IR (neat) 3288 (br), 2974 (m), 1716 (S), 1666 (s), 1499 (m), 1456 (m), 1392 (m), 1242 (s), 1161 (s), 1124 (w), 1078 (w), 999 (w), 735 (m), 700 (m).

^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 7.43-7.15 (m, br), 5.69 (m, br), 5.43-4.91 (m, br), 4.76-4.07 (m, br), 3.64 (m, br), 3.54 (m, br), 3.20-3.03 (m, br), 3.02 (s), 2.95-2.70 (m, br), 2.03 (m, br), 1.65 (d, br, J = 6.9 Hz), 1.40 (s), 1.39 (s), 1.34 (s), 1.25-1.12 (m, br), 0.88 (m).

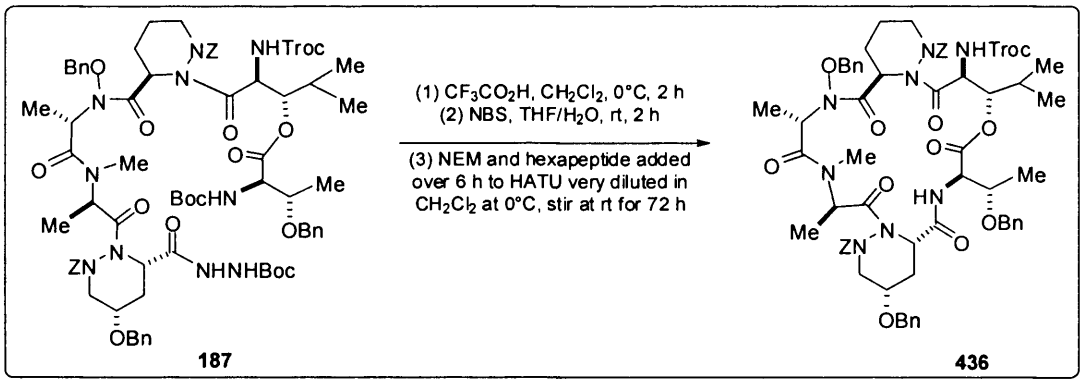
^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 171.9, 171.0, 170.0, 168.6, 157.9, 156.3, 156.0, 155.7, 155.2, 154.6, 154.0, 153.3, 138.0, 137.7, 135.8, 134.4, 128.4, 128.3, 127.5, 127.3, 81.2, 79.9, 78.8, 74.7, 70.6, 69.8, 68.8, 68.4, 58.2, 52.4, 51.1, 50.1, 48.4, 47.2, 45.6, 30.5, 28.7, 28.1, 24.5, 19.7, 17.3, 16.7, 16.5, 16.2, 15.9, 15.7, 13.9.

The two compounds obtained were analysed separately by Mass Spectroscopy

FAB (+) HRMS: Calcd. for $C_{77}Cl_3H_{97}N_{10}NaO_{20}$: $(M+Na)^+$: *m/e* 1609.58436; Found: *m/e* 1609.59520.

FAB (+) HRMS: Calcd. for $C_{77}Cl_3H_{97}N_{10}NaO_{20}$: $(M+Na)^+$: *m/e* 1609.58436; Found: *m/e* 1609.59929.

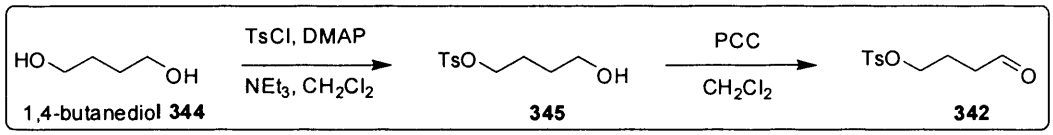
Cyclodepsipeptide 436



To depsipeptide **187** (1.45 g, 0.912 mmol) in dry CH_2Cl_2 (14.1 mL) at 0 °C under N_2 was added in one portion CF_3CO_2H (14.1 mL, 182 mmol). The reaction mixture was stirred for 2 h at 0 °C, concentrated *in vacuo*, co-evaporated from toluene (2 x 10 mL) to remove the excess CF_3CO_2H. To the residue in THF (10.2 mL) and H_2O (10.2 mL) was added NBS (0.32 g, 1.82 mmol) portionwise over 10 min. The reaction mixture was stirred at rt for 2 h, diluted with EtOAc (50mL) and washed with brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a white foam. To a suspension of HATU (3.47 g, 9.12 mmol) in dry CH_2Cl_2 (1 L) at 0°C and under N_2 was added dropwise over 5 h, a solution of the above crude product and *N*-ethylmorpholine (1.56 mL, 12.3 mmol) in dry CH_2Cl_2 (1 L). The reaction mixture was stirred at rt for 60 h. The reaction mixture was concentrated *in vacuo* and the yellow residue dissolved in EtOAc (500 mL), washed with 1M aq. HCl (2 x 150 mL), 5% aq. $NaHCO_3$ (2 x 150 mL) and brine (150 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by SiO_2 flash chromatography (gradient elution 4:1 to 1:2 petrol:EtOAc) but no product could be isolated.

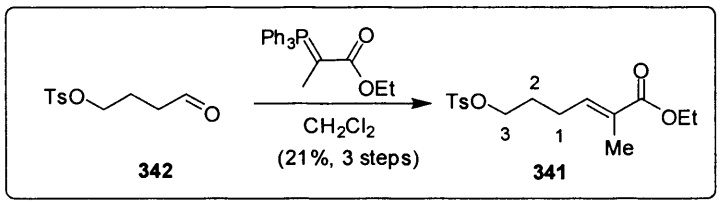
9. Toward the Synthesis of (+)-Allopumiliotoxin 339A

Aldehyde 342



To a 250-mL round-bottomed flask were added 1,4-butanediol (20 g, 0.222 mol, 7.7 eq), NEt_3 (4.2 mL, 0.0303 mol, 1.05 eq), DMAP (128 mg, 0.04 eq) and recrystallised TsCl (5.50 g, 0.0288 mol, 1 eq). The reaction mixture was stirred at rt for 1.5 h before being added to a separating funnel containing CH_2Cl_2 (160 mL) and HCl (8 mL of 37% HCl and 112 mL of H_2O). The aqueous layer was extracted with CH_2Cl_2 (100mL), combined organic layers were washed with water, dried ($MgSO_4$), and concentrated *in vacuo*. To the crude oil in CH_2Cl_2 (600 mL) was added PCC (6.21 g, 0.0288 mol, 1 eq). The reaction mixture was stirred at rt for 2.5 h and concentrated *in vacuo*. The obtained slurry was very rapidly purified by SiO_2 flash chromatography (gradient elution 6:1 to 3:1 petrol:EtOAc); the unstable aldehyde **342** was obtained as a yellow oil. Aldehyde **342**, which was not characterised any further, was used immediately for the next step as described below.[86]

Alkene 341



To aldehyde **342** in CH_2Cl_2 (30 mL) was added carbethoxyethylidene triphenylphosphorane (10.44 g, 0.0288 mol, 1 eq). The reaction mixture was stirred at rt for 20 h and concentrated *in vacuo*. The crude residue was purified by SiO_2 flash chromatography (gradient elution 10:1 to 6:1 petrol:EtOAc) to afford alkene **341** as a yellow oil (1.95 g, 21 % over 3 steps).

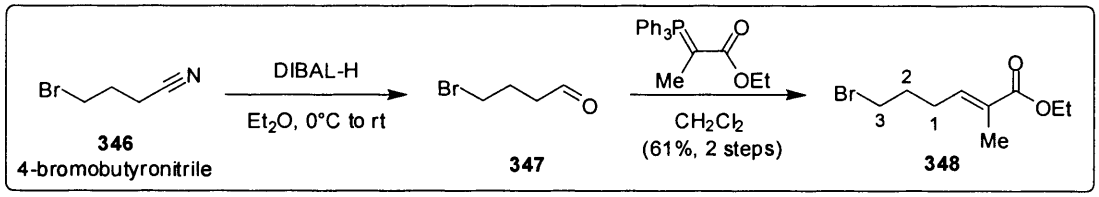
IR (neat film) 2982 (m), 1707 (s), 1649 (m), 1599 (m), 1447 (m), 1364 (s), 1267 (s), 1176 (s), 1134 (m), 1097 (m), 1007 (w), 932 (m), 816 (m), 744 (m) 663 (s) 577 (m), 555 (s).

^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 7.71 (ddd, *J* = 8.4, 3.7, 2.0 Hz, 2 H, Ph), 7.28 (d, *J* = 8.5 Hz, 2 H, Ph), 6.54 (tq, *J* = 7.5, 1.3 Hz 1 H, $\underline{H}C=C$), 4.10 (q, *J* = 7.2 Hz, 2 H, $OC\underline{H}_2$), 3.97 (t, *J* = 6.2 Hz, 2 H, H3), 2.38 (s, 3 H, $C\underline{H}_3$-Ar), 2.14 (dd, *J* = 14.2, 7.4 Hz, 2 H, H1), 1.73 (m, 2 H, H2), 1.71 (s, 3 H, $CH=CC\underline{H}_3$), 1.21 (s, 3 H, $OCH_2C\underline{H}_3$).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 167.6 ($\underline{C}=O$), 144.7 (C Ar), 139.3 ($\underline{C}H=C$), 132.5 (C Ar), 129.7 (CH Ar), 129.0 ($\underline{C}(CH_3)$), 127.7 ($\underline{C}H$ Ar), 69.5 (C3), 60.3 ($O\underline{C}H_2CH_3$), 27.6 (C1), 24.3 (C2), 21.4 ($\underline{C}H_3$-Ar), 14.1 ($C=C(\underline{C}H_3)$), 12.2 ($OCH_2\underline{C}H_3$).

FAB (+) HRMS: Calcd. for $C_{16}H_{22}NaO_5S$: $(M+Na)^+$: *m/e* 349.10856; Found: *m/e* 349.10794.

Alkene 348



346 4-bromobutyronitrile

347

348

To a three-necked, round-bottomed flask, equipped with an addition funnel and containing 4-bromobutyronitrile **346** (20 g, 13.51 mL, 0.135 mol) and ether (135 mL) was added dropwise over 0.5 h at 0 °C a solution of DIBAL-H (1 M in hexane, 175 mL, 0.175 mol). The mixture was stirred at 0 °C for 2 h and at rt for 0.5 h, and then was slowly added to a precooled (0 °C) 10% aq. H_2SO_4 (250 mL). The resulting solution was stirred for 1 h and extracted with Et_2O (2 x 250 mL). The combined organic layers were washed with water and brine, dried ($MgSO_4$), and concentrated *in vacuo* (water bath at 28 °C, aldehyde **347** is volatile). To the crude oil in CH_2Cl_2 (135 mL) was added carbethoxyethylidene triphenylphosphorane (48.9 g, 0.135 mol, 1 eq). The reaction mixture was stirred at rt for 20 h, concentrated *in vacuo* and the crude residue was purified by SiO_2 flash chromatography (gradient elution 30:1 to 10:1 petrol:EtOAc) affording the title compound **348** as a yellow oil (19.29 g, 61 % over 2 steps).[88]

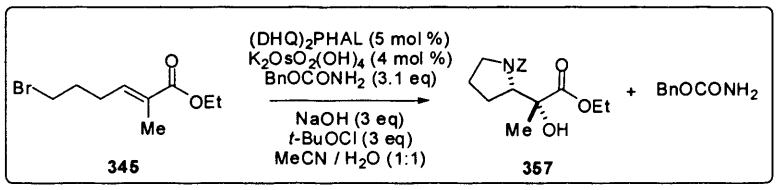
IR (neat film) 3402 (w), 2978 (m), 1713 (s), 1651 (m), 1443 (m), 1365 (w), 1280 (br), 1111 (m).

^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 6.68 (tq, *J* = 7.4, 1.3 Hz, 1 H, HC=C), 4.17 (q, *J* = 7.2 Hz, 2 H, CH_2O), 3.40 (t, *J* = 6.5 Hz, 2 H, H3), 2.33 (ddd, *J* = 14.7, 7.5, 0.6 Hz, 2 H, H1), 1.99 (m, 2 H, H2), 1.84 (s, 3 H, $CH=CCH_3$), 1.30 (t, *J* = 7.2 Hz, 3 H, CH_3CH_2O).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 168.0 (C=O), 139.6 (HC=C), 129.3 (CH=C), 60.5 (CH_2O), 33.0 (C3), 31.4 (C2), 27.0 (C1), 14.3 (CH_3CH_2O) 12.5 ($CH=CCH_3$).

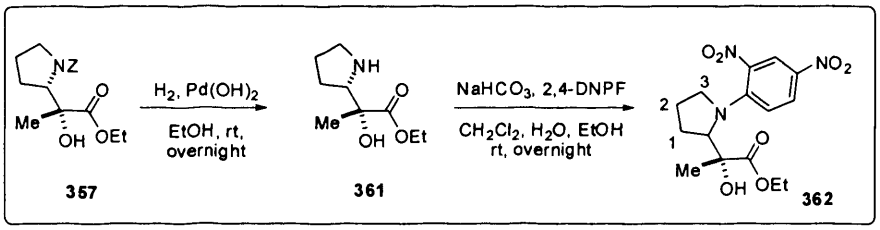
FAB (+) HRMS: Calcd. for $C_9BrH_{15}NaO_2$: $(M+Na)^+$: *m/e* 257.01531; Found: *m/e* 257.01563.

Alcohol 357



To benzylcarbamate (940 mg, 6.2 mmol) in MeCN (5 mL) at rt was added a freshly prepared solution of NaOH (0.244 g of NaOH in 10 mL of water) followed by a freshly prepared solution of *tert*-butylhypochlorite (0.66 mL, 6.10 mmol). Then a solution of the ligand $(DHQD)_2PHAL$ (77 mg, 0.059 mmol) in MeCN (5 mL) was added followed by olefin **347** (500 mg, 2.00 mmol) and the osmium catalyst. (29 mg, 0.079 mmol). The reaction mixture was stirred at rt for 24 h and did not go to competion according to TLC analysis. It was then quenched with saturated sodium sulfite (10 mL). The two phases were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and concentrated. Purification by chromatography (gradient elution petrol:EtOAc 30:1 to 20:1) provided **357** contaminated by benzylcarbamate (100 mg). The mixture which was not characterised any further was used directly for the next step as described below.

Alcohol 362



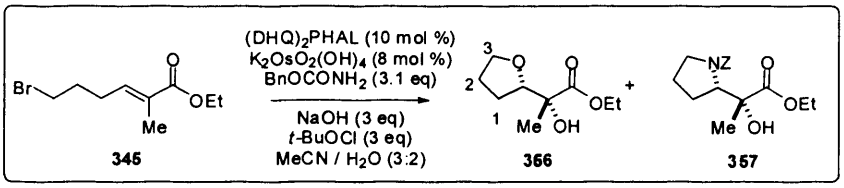
To a mixture of alcohol **357** and benzylcarbamate (100 mg) in EtOH (10 mL) under N_2 was added $Pd(OH)_2$ (20% wet, 10 mg). The flask was purged and the N_2 balloon was replaced by a H_2 balloon. The mixture was stirred rigorously for 20 h. The suspension was filtered through a pad of Celite® and the solvent concentrated *in vacuo*. To the crude residue in CH_2Cl_2 (1 mL), H_2O (1 mL), and EtOH (2 mL) was added $NaHCO_3$ (250 mg, 3 mmol) and dinitrofluorobenzene (0.38 mL, 3 mmol). The reaction mixture was stirred at rt overnight and extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and filtered. The solvent was then removed *in vacuo* and the crude residue was purified by SiO_2 flash chromatography (gradient elution 20:1 to 5:1 petrol:EtOAc) affording **362** as a yellow oil (55 mg).

^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 8.69 (d, *J* = 2.7 Hz, 1 H, Ar), 8.10 (dd, *J* = 9.5, 2.7 Hz, 1 H, Ar), 7.22 (d, *J* = 9.5 Hz, 1 H, Ar), 4.60 (t, *J* = 7.2 Hz, 1 H, C<u>H</u>-N), 3.92 (dd, *J* = 14.3, 7.2 Hz, 1 H, C<u>H</u>$_2$-O), 3.82 (dd, *J* = 14.3, 7.2 Hz, 2 H, C<u>H</u>$_2$-O), 3.58 (td, *J* = 10.4, 6.4 Hz, 1 H, H3), 2.73 (m, 1 H, H3), 2.20 (m, 2 H, H1), 2.05 (m, 1 H, H2), 1.71 (m, 1 H, H2), 1.39 (s, 3 H,CC<u>H</u>$_3$), 1.13 (t, 3 H, C<u>H</u>$_3$CH$_2$O).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 174.8 (<u>C</u>=O), 147.4 (Ar), 137.1 (Ar) , 136.9 (Ar), 126.8 (Ar), 123.7 (Ar), 117.8 (Ar), 68.1 (<u>C</u>HN), 64.1 (<u>C</u>H$_2$-O), 62.3 (C3), 25.5 (C1), 25.1 (C2), 21.9 (C(<u>C</u>H$_3$)), 13.7 (<u>C</u>H$_3$CH$_2$O).

FAB (+) HRMS: Calcd. for $C_{15}H_{19}NaN_3O_7$: $(M+Na)^+$: *m/e* 376.11206; Found: *m/e* 376.11254.

Tetrahydrofuran 366



To benzylcarbamate (1.99 g, 13.2 mmol) in MeCN (17 mL) at rt was added a freshly prepared solution of NaOH (0.50 g of NaOH in 20 mL of water) followed by freshly prepared *tert*-butylhypochlorite (1.43 g, 13.0 mmol). Then a solution of the ligand $(DHQD)_2PHAL$ (0.33 g, 0.425 mmol) in MeCN (17 mL) was added followed by olefin **345** (1 g, 4.25 mmol) and the osmium catalyst (0.125 g, 0.340 mmol). The reaction mixture was stirred at rt for 20 h and quenched with saturated sodium sulfite. The two phases were separated and the aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Extensive purification by SiO_2 flash chromatography (gradient elution 30:1 to 10:1 petrol:EtOAc) followed by preparative chromatography provided the nearly pure dihydroxylated product **366** in order to carry out analysis.

Data for **366**: IR (neat film) 3510 (m), 2982 (s), 2878 (m), 1736 (s), 1454 (w), 1373 (w), 1259 (m), 1203 (m), 1136 (m), 1072 (m), 1024 (w).

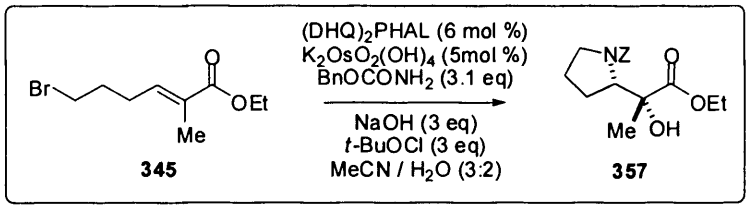
^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 4.17 (qd, *J* = 10.7, 7.0 Hz, 2 H, C$\underline{H}_2$O), 4.02 (t, *J* = 7.0 Hz 1 H, C$\underline{H}$-O), 3.77 (m, 1 H, H3), 3.69 (m, 1 H, H3), 3.14 (br, 1 H, O$\underline{H}$), 1.83 (m, 4 H, H1, H2), 1.22 (s, 3 H, C$\underline{C}H_3$) 1.21 (t, *J* = 7.0 Hz, 3 H, C$\underline{H}_3$CH$_2$O).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 175.6 ((OEt)-$\underline{C}$=O), 82.9 ($\underline{C}$H-O), 75.6 ($CH_3\underline{C}$OH), 69.2 (C3), 61.6 ($\underline{C}H_2O$), 26.0 (C1), 25.1 (C2), 21.4 (HO-C$\underline{C}H_3$), 13.9 ($\underline{C}H_3CH_2O$).

FAB (+) HRMS: Calcd. for $C_9H_{17}O_4$: $(M+H)^+$: *m/e* 189.11268; Found: *m/e* 189.11286.

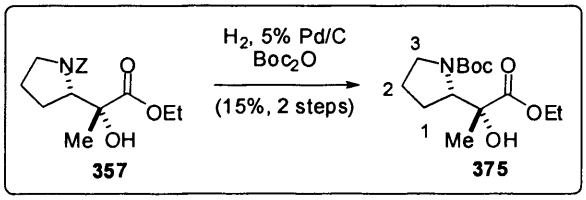
Improved procedure for Sharpless Asymmetric Aminohydroxylation[93]

Alcohol 357



To benzylcarbamate (11.15 g, 73.8 mmol) in MeCN (90 mL) at rt was added a freshly prepared solution of NaOH (2.9 g of NaOH in 112 mL of water, 72 mmol) followed by freshly prepared *tert*-butylhypochlorite[91] (7.87 g, 72 mmol). Then a solution of the ligand $(DHQ)_2PHAL$ (1.11 g, 1.4 mmol) in MeCN (90 mL) was added (It is important that the ligand be completely dissolved in MeCN) and the reaction mixture was cooled to 0 °C. Then olefin **345** was added (5.6 g, 23.8 mmol) followed by the osmium catalyst that was added by portion over 20 min (0.439 g, 1.19 mmol). The reaction mixture was stirred at 0 °C for 30 min and at rt for 2 h and quenched with saturated sodium sulfite (150 mL). The two phases were separated and the aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic phases were washed with brine (150 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by SiO_2 flash chromatography (gradient elution 30:1 to 20:1 petrol:EtOAc) provided alcohol **357** contaminated by some excess benzylcarbamate. Intermediate **357** was not characterised any further and was used immediately for the next step described below.

Alcohol 375



To a mixture of the alcohol **357** contaminated by some benzylcarbamate (7.8 g) in EtOH (100 mL) under N_2 was added Pd/C (10% wet, 2.0 g) and Boc_2O (7.3 g, 35.7 mmol). The flask was purged and the N_2 balloon was replaced by a H_2 balloon. The mixture was stirred rigorously overnight. The suspension was filtered through a pad of Celite® and the solvent concentrated *in vacuo*. The resulting oil was purified by SiO_2 flash chromatography (gradient elution 20:1 to 10:1 petrol:EtOAc) affording the title compound **375** as a colorless oil (1.05 g, 15 % over 2 steps).[94]

$[\alpha]_D$ - 16.8° (*c* 0.34, CH_2Cl_2).

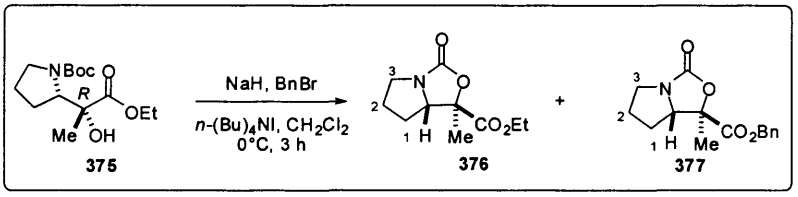
IR (neat film) 3512 (m), 3342 (w), 2978 (s), 1730 (s), 1697 (s), 1454 (w), 1392 (s), 1257 (m), 1171 (s), 1119 (m), 1078 (w), 1024 (w).

^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 4.54 (br, 1 H, OH), 4.19 (m, 1 H, CH_2O), 4.14 (m, 1H, N-CH), 4.09 (m, 1 H, CH_2O), 3.50 (br, 1 H, H3), 3.20 (m, 1 H, H3), 1.86 (m, 3 H, H2, H1), 1.67 (m, 1 H, H2), 1.39 (s, 9 H, $C(CH_3)_3$), 1.27 (s, 3 H, CCH_3) 1.20 (t, *J* = 7.0 Hz, 3 H, CH_3CH_2O).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 175.1 (COOEt), 156.3 (O=C-O($C(CH_3)_3$), 80.0 ($C(CH_3)_3$), 77.2 (CH_3COH), 63.3 (CHNH), 61.7 (CH_2O), 48.0 (C3), 28.3 ($C(CH_3)_3$), 26.8 (C1), 24.4 (C2), 20.6 (HO-CCH_3), 14.0 (CH_3CH_2O).

FAB (+) HRMS: Calcd. for $C_{44}H_{49}N_5NaO_9$: $(M+Na)^+$: *m/e* 310.16303; Found: *m/e* 310.16196.

Mixture of 376 and 377



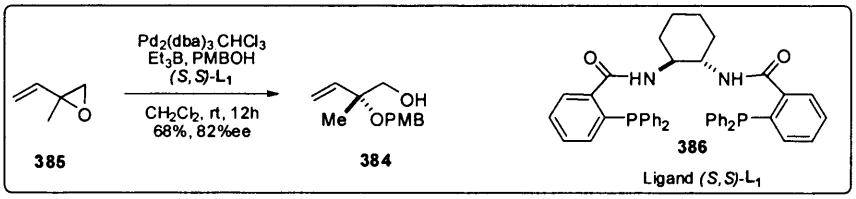
To a solution of **375** (100 mg, 0.311 mmol) in THF (1.5 mL) at 0 °C under N_2 was added NaH (60% suspension in oil, 12.5 mg, 0.311 mmol). After 10 min at 0 °C, *n*-(Bu_4)NI (11.5 mg, 0.031 mmol) was added followed by BnBr (0.040 mL, 0.311 mmol). The reaction was warmed to rt and stirred for 3 h. It was then slowly quenched with water (3 mL) and extracted with EtOAc (3 x 10 mL). The resulting oil was purified by SiO_2 flash chromatography (gradient elution 10:1 to 2:1 petrol:EtOAc) affording an inseparable mixture of **376** and **377** (55 mg) in proportion 2:1.

^{1}H-NMR (500 MHz, $CDCl_3$, 298K) **376** δ 7.37-7.31 (m, 5 H, Ar), 5.24 (d, *J* = 12.4 Hz, 1 H, PhCH_2O), 5.21 (d, *J* = 12.4 Hz, 1 H, PhCH_2O), 3.96 (m, 1 H, CH-N), 3.63 (m, 1 H, H3), 3.18 (m, 1 H, H3), 2.07 (m, 1 H, H2), 2.07 (m, 2 H, H2, H1), 1.58 (s, 3 H, CCH_3), 1.50 (m, 1 H, H1); **377** δ 4.25 (qd, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 3.96 (m, 1 H, CH-N), 3.63 (m, 1 H, H3), 3.18 (m, 1 H, H3),

2.07 (m, 1 H, H2), 2.07 (m, 2 H, H2, H1), 1.58 (s, 3 H, CC<u>H</u>$_3$), 1.50 (m, 1 H, H1), 1.30 (t, J = 12.4 Hz, 3 H, C<u>H</u>$_3$CH$_2$O).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 172.1, 171.8 (<u>C</u>=O), 160.2, 160.1 (<u>C</u>=O), 134.9, 128.7, 126.6, 128.1 (Ar), 80.2, 67.8 (PhC<u>H</u>$_2$O), 66.2, 66.1 (<u>C</u>HN), 62.4 (O-<u>C</u>H$_2$CH$_3$), 46.0 (C3), 26.1 (C1), 24.9 (C2), 19.2 (C(<u>C</u>H$_3$)), 14.0 (<u>C</u>H$_3$CH$_2$O).

Alcohol 384



To a 2 L round bottomed flask containing $(dba)_3Pd_2.CHCl_3$ (0.749 g, 0.723 mmol), chiral ligand (*S,S*)-L$_1$ **386** (1.5 g, 2.17 mmol) and PMB-OH (9.05 mL, 72.3 mmol) was added dry CH_2Cl_2 (720 mL) at rt under N_2. The resulting dark purple mixture was stirred at rt until it turned a deep orange color (roughly 15 min). Triethylborane (1 M solution in THF, 0.723 mL, 0.723 mmol) was added followed by 2-methyl-2-vinyloxirane **385** (8.04 mL, 72.3 mmol). The reaction mixture was stirred for 20 h. The solvent was removed *in vacuo* and the crude product was purified by SiO_2 flash chromatography (gradient elution 30:1 to 10:1 petrol:EtOAc) affording alcohol **384** as a yellow oil (11.00 g, 68 %, 82% ee).[97]

$[\alpha]_D$ + 18.1° (*c* 0.21, CH_2Cl_2).

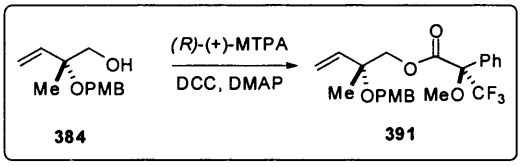
IR (neat film) 3440 (br), 2933 (br), 1726 (s), 1612 (m), 1514 (s), 1460 (w), 1412 (w), 1379 (w), 1248 (s), 1174 (w), 1115 (m), 1038 (m), 929 (w), 822 (m), 733 (m).

^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 7.23 (d, J = 8.6 Hz, 2 H, Ar), 6.86 (d, J = 8.6 Hz, 2 H, Ar), 5.90 (dd, J = 17.6, 10.9 Hz, 1 H, C<u>H</u>=CH$_2$), 5.32 (dd, J = 17.5, 1.1 Hz, 1 H, CH=C<u>H</u>$_2$), 5.42 (dd, J = 11.0, 1.1 Hz, 1 H, CH=C<u>H</u>$_2$), 4.32 (s, 2 H, O-C<u>H</u>$_2$-Ar), 3.78 (s, 3 H, OC<u>H</u>$_3$), 3.52 (dd, J = 11.1, 5.0 Hz, 1 H, C<u>H</u>$_2$-OH), 3.45 (dd, J = 11.1, 6.4 Hz, 1 H, C<u>H</u>$_2$-OH), 2.10 (t, J = 6.4 Hz, 1 H, O<u>H</u>), 1.36 (s, 3 H, C<u>H</u>$_3$).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 159.0 (Ar), 139.5 (<u>C</u>H=CH_2), 131.0 (Ar), 129.0 (Ar), 117.1 (CH=<u>C</u>H_2), 113.3 (Ar), 78.3 (Me<u>C</u>OPMB), 69.5 (<u>C</u>H_2-OH), 65.8 (O-<u>C</u>H_2-Ar), 55.2 (O<u>C</u>H_3), 18.6 (<u>C</u>H_3).

FAB (+) HRMS: Calcd. for $C_{13}H_{18}NaO_3$: $(M+Na)^+$: *m/e* 245.11536; Found: 245.11588.

Ester 391



To alcohol **384** (50 mg, 0.227 mmol) and (*R*)-(+)-MTPA (53 mg, 0.227 mmol) was added at rt under N_2, CH_2Cl_2 (0.8 mL) followed by DCC (47 mg, 0.227 mmol) and DMAP (2.8 mg, 0.023 mmol). The reaction mixture was stirred at rt overnight but did not go to completion according to TLC analysis. The solvent was removed *in vacuo* and the crude product was purified by SiO_2 flash chromatography (10:1 petrol:EtOAc) to isolate ester **391** (55 mg, 56%), the faster moving product of the TLC as yellow oil. ^{19}F NMR of the mixture showed a 100:10 mixture of diastereoisomers (82% ee).

$[\alpha]_D$ + 33.1° (*c* 0.56, CH_2Cl_2).

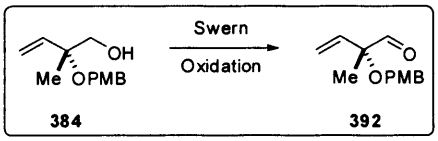
IR (neat film) 2947 (m), 2849 (w), 1753 (s), 1612 (w), 1512 (m), 1454 (w), 1379 (w), 1250 (s), 1175 (s), 1119(m), 1032 (s), 822 (w), 719 (w).

^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 7.53 (d, *J* = 8.0 Hz, 2 H, Ar), 7.36 (m, 1 H, Ar), 7.29 (m, 2 H, Ar), 7.18 (d, *J* = 8.7 Hz, 2 H, Ar(PMB)), 6.83 (d, *J* = 8.7 Hz, 2 H, Ar(PMB)), 5.84 (dd, *J* = 17.4, 11.4 Hz, 1 H, C<u>H</u>=CH_2), 5.32 (dd, *J* = 11.4, 0.9, 1 H, CH=C<u>H</u>$_2$), 5.29 (dd, *J* = 17.4, 0.9 Hz, 1 H, CH=C<u>H</u>$_2$), 4.39 (d, *J* = 11.2 Hz, 1 H, C<u>H</u>$_2$-OC=O), 4.32 (s, 2 H, OC<u>H</u>$_2$Ar), 4.25 (d, *J* = 11.2 Hz, 1 H, C<u>H</u>$_2$-OC=O), 3.78 (s, 3 H, ArC<u>H</u>$_3$), 3.52 (s, 3 H, $_3$FCCOC<u>H</u>$_3$), 1.38 (s, 3 H, C<u>H</u>$_3$).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 166.3 (C=O), 158.9 (Ar), 138.9 (<u>C</u>H=CH_2) , 132.2 (Ar), 130.9 (Ar), 129.5 (Ar), 128.7 (Ar), 128.3 (Ar), 127.5 (Ar), 117.7 (CH=<u>C</u>H_2), 113.7 (Ar), 84.6 (q, <u>C</u>F_3), 76.4 (Me<u>C</u>OPMB), 70.8 (<u>C</u>H_2-OC=O), 65.8 (O-<u>C</u>H_2-Ar), 55.4 (O<u>C</u>H_3), 55.3 (O<u>C</u>H_3), 19.7 (<u>C</u>H_3).

FAB (+) HRMS: Calcd. for $C_{23}H_{25}F_3NaO_5$: $(M+Na)^+$: *m/e* 451.15517; Found: 461.15438.

Aldehyde 392



384 **392**

To a stirred solution of DMSO (19.9 mL, 280 mmol) in dry CH_2Cl_2 (287 mL) at -78° C under N_2 was added $(COCl)_2$ (12.2 mL, 140 mmol) dropwise over 5 min. The reaction mixture was stirred at -78 °C under N_2 for 20 min and a solution of alcohol **384** (10.38 g, 46.7 mmol) in dry CH_2Cl_2 (97 mL) was added *via* canula over 15 min. The reaction mixture was stirred at -78 °C for 30 min and freshly distilled NEt_3 (98.3 mL, 700 mmol) was added dropwise, the mixture was allowed to warm to rt over 20 min and was then quenched with brine (150 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude aldehyde **392** which was used without further purification.

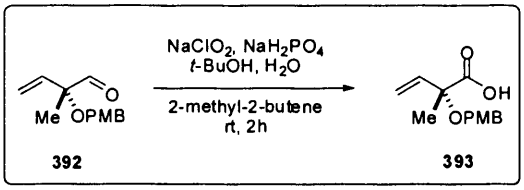
An analytical sample was purified by SiO_2 flash chromatography (gradient elution 20:1 to 10:1 petrol:EtOAc) affording the title compound **392** as a yellow oil.

^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 9.49 (s, 1 H, CHO), 7.28 (d, *J* = 8.7 Hz, 2 H, Ar), 6.87 (d, *J* = 8.7 Hz, 2 H, Ar), 5.81 (dd, *J* = 17.6, 10.8 Hz, 1 H, C<u>H</u>=CH_2), 5.46 (dd, *J* = 17.6, 0.9 Hz, 1 H, CH=C<u>H</u>$_2$), 5.42 (dd, *J* = 10.8, 0.9 Hz, 1 H, CH=C<u>H</u>$_2$), 4.46 (d, *J* = 10.8 Hz, 1 H, C<u>H</u>$_2$-O), 4.40 (d, *J* = 10.8 Hz, 1 H, C<u>H</u>$_2$-O), 3.79 (s, 3 H, OC<u>H</u>$_3$), 1.45 (s, 3 H,C<u>H</u>$_3$).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 200.7 (<u>C</u>HO), 159.3 (Ar), 135.5 (<u>C</u>H=CH_2), 130.2 (Ar), 129.3 (Ar), 119.1 (CH=<u>C</u>H_2), 113.9 (Ar), 83.4 (Me<u>C</u>OPMB), 65.8 (<u>C</u>H_2-O), 55.3 (O<u>C</u>H_3), 18.7 (CH_3).

FAB (+) HRMS: Calcd. for $C_{13}H_{16}NaO_3$: $(M+Na)^+$: *m/e* 243.09971; Found: *m/e* 243.09876.

Acid 393



To the crude aldehyde **392** (46.7 mmol) in *t*-BuOH (140 mL) and 2-methyl-2-butene, were added simultaneously over 15 min at rt a solution of $NaClO_2$ (12.7 g, 140 mmol) and a solution of NaH_2PO_4 (16.79 g, 140 mmol) in water (140 mL). The reaction mixture was stirred at rt for 2 h, then diluted with sat. aq. NH_4Cl (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude carboxylic acid **393** which was used without further purification. An analytical sample was purified by SiO_2 flash chromatography (gradient elution 5:1 to 1:2 petrol:EtOAc) affording the title compound **393** as a colorless oil.

$[\alpha]_D$ + 11.0° (*c* 0.63, CH_2Cl_2).

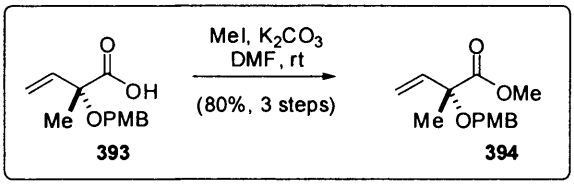
IR (neat film) 3180 (br), 2995 (m), 2943 (m), 1718 (s), 1612 (m), 1514 (s), 1458 (w), 1381 (w), 1248 (s), 1120 (m), 1034 (m), 933 (w), 822 (m).

^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 9.96 (s, broad, 1 H, COOH), 7.28 (d, *J* = 8.7 Hz, 2 H, Ar), 6.87 (d, *J* = 8.7 Hz, 2 H, Ar), 6.01 (dd, *J* = 17.4, 10.7 Hz, 1 H, C<u>H</u>=CH_2), 5.49 (dd, *J* = 17.6, 0.9 Hz, 1 H, CH=C<u>H</u>$_2$), 5.39 (dd, *J* = 10.8, 0.9 Hz, 1 H, CH=C<u>H</u>$_2$), 4.47 (d, *J* = 10.4 Hz, 1 H, C<u>H</u>$_2$-O), 4.43 (d, *J* = 10.4 Hz, 1 H, C<u>H</u>$_2$-O), 3.79 (s, 3 H, OC<u>H</u>$_3$), 1.64 (s, 3 H,C<u>H</u>$_3$).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 176.2 (<u>C</u>OOH), 159.3 (Ar), 136.9 (<u>C</u>H=CH_2), 129.7 (Ar), 129.4 (Ar), 118.3 (CH=<u>C</u>H$_2$), 113.9 (Ar), 80.4 (Me<u>C</u>OPMB), 66.5 (<u>C</u>H$_2$-O), 55.3 (O<u>C</u>H$_3$), 21.9 (<u>C</u>H$_3$).

FAB (+) HRMS: Calcd. for $C_{13}H_{16}NaO_4$: $(M+Na)^+$: *m/e* 237.11268; Found: *m/e* 237.11215.

Ester 394



To a solution of the crude acid **393** (47.6 mmol) in dry DMF (155 mL) at rt under N_2 was added K_2CO_3 (32.2 g, 233 mmol) followed by MeI (291 mL, 467 mmol) over 10 min. The reaction mixture was stirred at rt for 3 h then quenched by addition of water (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with water (3 x 100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by SiO_2 flash column chromatography (gradient elution 30:1 to 20:1 petrol:EtOAc) afforded ester **394** as a yellow oil (9.39 g, 80%, 3 steps).

$[\alpha]_D$ + 9.54° (*c* 1.05, CH_2Cl_2).

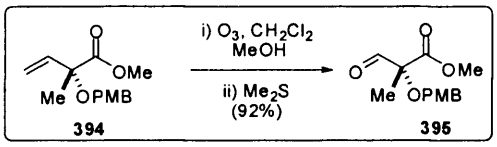
IR (neat film) 2995 (m), 2851 (m), 2908 (w), 2874 (w), 2837 (w), 1740 (s), 1612 (m), 1514 (s), 1460 (m), 1381 (w), 1300 (w), 1250 (s), 1201 (w), 1176 (w), 1117 (s), 1034 (m), 935 (w), 824 (m).

^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 7.30 (d, *J* = 8.7 Hz, 2 H, Ar), 6.85 (d, *J* = 8.7 Hz, 2 H, Ar), 6.06 (dd, *J* = 17.4, 10.7 Hz, 1 H, C<u>H</u>=CH_2), 5.41 (dd, *J* = 17.5, 0.9 Hz, 1 H, CH=C<u>H</u>$_2$), 5.29 (dd, *J* = 10.8, 0.9 Hz, 1 H, CH=C<u>H</u>$_2$), 4.45 (d, *J* = 10.6 Hz, 1 H, C<u>H</u>$_2$-O), 4.41 (d, *J* = 10.6 Hz, 1 H, C<u>H</u>$_2$-O), 3.77 (s, 3 H, OC<u>H</u>$_3$), 3.76 (s, 3 H, OC<u>H</u>$_3$), 1.58 (s, 3 H,C<u>H</u>$_3$).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 173.3 (COO<u>C</u>H$_3$), 159.0 (Ar), 138.2 (<u>C</u>H=CH_2) , 130.6 (Ar), 129.1 (Ar), 116.5 (CH=<u>C</u>H$_2$), 113.6 (Ar), 80.5 (Me<u>C</u>OPMB), 66.6 (<u>C</u>H$_2$-O), 55.2 (O<u>C</u>H$_3$), 52.2 (O<u>C</u>H$_3$), 23.3 (<u>C</u>H$_3$).

FAB (+) HRMS: Calcd. for $C_{14}H_{19}O_4$: $(M+H)^+$: *m/e* 251.12833; Found: *m/e* 251.12869.

Aldehyde 395



A mixture of alkene **395** (1.0 g, 4.0 mmol) in CH_2Cl_2 (25mL) and MeOH (1.25 mL) at -78 °C was purged with O_2 for 30 s and O_3 was bubbled into the flask until the mixture turned blue. Residual ozone was flushed out with nitrogen and Me_2S (2.22 mL, 40 mmol) was added at -78 °C. The reaction mixture was warmed to rt, stirred for 30 min and concentrated *in vacuo*. Purification by SiO_2 flash column chromatography (gradient elution 7:1 to 2:1 petrol:EtOAc) afforded aldehyde **395** as a yellow oil (0.94 g, 92%).

$[\alpha]_D$ - 3.16 ° (*c* 0.28, CH_2Cl_2).

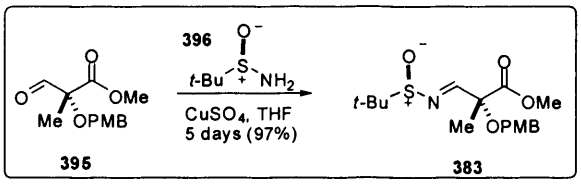
IR (neat film) 3447 (br), 2955 (m), 2841 (w), 1736 (s), 1688 (w), 1606 (m), 1514 (s), 1458 (m), 1254 (s), 1157 (m, br), 1032 (m), 827 (m).

^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 9.64 (s, 1 H, C<u>H</u>O), 7.32 (d, *J* = 8.7 Hz, 2 H, Ar), 6.87 (d, *J* = 8.7 Hz, 2 H, Ar), 4.54 (d,*J* = 10.4 Hz, 1 H, C<u>H</u>$_2$-O), 4.50 (d, *J* = 10.4 Hz, 1 H, C<u>H</u>$_2$-O), 3.79 (s, 3 H, COOC<u>H</u>$_3$), 3.78 (s, 3 H, OC<u>H</u>$_3$), 1.58 (s, 3 H,C<u>H</u>$_3$).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 197.3 (<u>C</u>HO), 169.6 (<u>C</u>OOCH$_3$), 159.5 (Ar), 129.6 (Ar), 129.3 (Ar), 113.9 (Ar), 84.8 (Me<u>C</u>OPMB), 67.8 (<u>C</u>H$_2$-O), 55.3 (O<u>C</u>H$_3$), 52.8 (COO<u>C</u>H$_3$), 18.3 (<u>C</u>H$_3$).

CI HRMS: Calcd. for $C_5H_{16}O_5$ *m/e* : 252.09977; Found: 252.09953.

Sulfinimine 383



To a solution of aldehyde **395** (1.87 g, 7.4 mmol) in dry CH_2Cl_2 (15 mL) at rt under N_2 was added anhydrous $CuSO_4$ (0.90 g, 7.4 mmol) followed by solid (*R*)-*tert*-butanesulfinamide (0.87 g, 7.4 mmol). The reaction mixture was stirred at rt for 5 days, then filtered through Celite® and concentrated *in vacuo*. The resulting oil (2.56 g) was used in the next step and was not purified any further. Therefore, the yield of the formation of sulfinimine **383** was assumed to be *ca.* 97%.[100]

$[\alpha]_D$ - 43.0° (*c* 0.52, CH_2Cl_2).

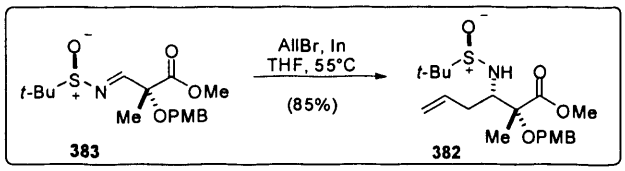
IR (neat film) 2955 (m), 1745 (s), 1618 (m), 1514 (s), 1456 (m), 1369 (w), 1250 (s), 1257 (br), 1032 (w), 827 (w).

^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 8.17 (s, 1 H, N=C<u>H</u>), 7.28 (d, *J* = 8.8 Hz, 2 H, Ar), 6.84 (d, *J* = 8.8 Hz, 2 H, Ar), 4.52 (d, *J* = 10.4 Hz, 1 H, C<u>H</u>$_2$-O), 4.50 (d, *J* = 10.4 Hz, 1 H, C<u>H</u>$_2$-O), 3.76 (s, 3 H, OC<u>H</u>$_3$), 3.75 (s, 3 H, OC<u>H</u>$_3$), 1.67 (s, 3 H, C<u>H</u>$_3$), 1.18 (s, 9 H, C(C<u>H</u>$_3$)$_3$).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 170.8 (COO<u>C</u>H$_3$), 167.1 (N=<u>C</u>H), 159.3 (Ar), 129.6 (Ar), 129.3 (Ar), 113.7 (Ar), 82.4 (Me<u>C</u>OPMB), 67.6 (<u>C</u>H$_2$-O), 57.7 (<u>C</u>(CH$_3$)$_3$), 55.2 (O<u>C</u>H$_3$), 52.5 (O<u>C</u>H$_3$), 22.4 (C(<u>C</u>H$_3$)$_3$), 21.2 (<u>C</u>H$_3$).

FAB (+) HRMS: Calcd. for $C_{17}H_{25}NNaO_5S$: $(M+Na)^+$: *m/e* 378.13511; Found: *m/e* 378.13362.

Alkene 382



To sulfinimine **383** (200 mg, 562 mmol) in dry THF (1.9 mL) at rt under N_2 was added Indium (84 mg, 731 mmol) followed by allylbromide (0.098 mL, 731 mmol) after 10 min. The reaction vessel was fitted with a reflux condenser and immersed for 40 min in an oil bath pre-heated to 55 °C. The reaction mixture was then cooled to rt, quenched with water (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by SiO_2 flash column chromatography (gradient elution 5:1 to 1:1 petrol:EtOAc) afforded alkene **382** as the major product of a mixture of 2 isomers in proportion 80/20 (189 mg, 85 %).[103]

IR (neat film) 3331 (w), 2951 (s), 1742 (s), 1612 (w), 1514 (m), 1462 (m), 1387 (w), 1250 (s), 1178 (w), 1119 (m), 1072 (s), 1037 (m), 912 (w), 820 (w).

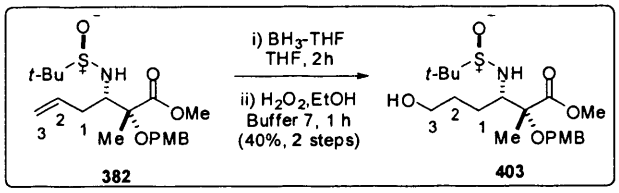
^{1}H-NMR (500 MHz, $CDCl_3$, 298K) *Major isomer (S)* δ 7.30 (d, *J* = 8.6 Hz, 2 H, Ar), 6.85 (d, *J* = 8.6 Hz, 2 H, Ar), 5.71 (m, 1 H, H$\underline{C}$=CH_2), 4.97 (m, 2 H, HC=C$\underline{H_2}$), 4.60 (d, *J* = 10.3 Hz, 1 H, C$\underline{H_2}$-O), 4.41 (d, *J* = 10.3 Hz, 1 H, C$\underline{H_2}$-O), 3.89 (d, *J* = 8.5 Hz, 1 H, N$\underline{H}$), 3.77 (s, 3 H, OC$\underline{H_3}$), 3.74 (s, 3 H, COOC$\underline{H_3}$), 3.53 (dt, *J* = 9.1, 3.5 Hz, 1 H, C$\underline{H}$-NH), 2.29 (m, 1 H, C$\underline{H_2}$CH), 2.15 (m, 1 H, C$\underline{H_2}$CH), 1.68 (s, 3 H, C$\underline{H_3}$C), 1.16 (s, 9 H, C(C$\underline{H_3}$)$_3$); *Minor isomer (R)* δ 7.27 (d, *J* = 8.6 Hz, 2 H, Ar), 6.84 (d, *J* = 8.6 Hz, 2 H, Ar), 5.94 (m, 1 H, H$\underline{C}$=CH_2), 5.09 (m, 2 H, HC=C$\underline{H_2}$), 4.59 (d, *J* = 10.3 Hz, 1 H, C$\underline{H_2}$-O), 4.42 (d, *J* = 10.3 Hz, 1 H, C$\underline{H_2}$-O), 3.81 (d, *J* = 8.6 Hz, 1 H, N$\underline{H}$), 3.77 (s, 3 H, OC$\underline{H_3}$), 3.68 (s, 3 H, COOC$\underline{H_3}$), 3.58 (m 1 H, C$\underline{H}$-NH), 2.56 (m, 1 H, C$\underline{H_2}$CH), 2.40 (m, 1 H, C$\underline{H_2}$CH), 1.50 (s, 3 H, C$\underline{H_3}$C), 1.12 (s, 9 H, C(C$\underline{H_3}$)$_3$).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) *Major isomer (S)* δ 173.8 ($\underline{C}$OOCH$_3$), 159.1 (Ar), 135.4 (H$\underline{C}$=CH_2), 130.5 (Ar), 129.2 (Ar), 117.3 (HC=$\underline{C}$H$_2$), 113.6 (Ar), 82.1 (Me$\underline{C}$OPMB), 66.5 ($\underline{C}$H$_2$-O), 63.5 ($\underline{C}$H-NH), 56.8 ($\underline{C}$(CH$_3$)$_3$), 55.2 (O$\underline{C}$H$_3$), 52.1 (COO$\underline{C}$H$_3$), 37.1 ($\underline{C}$H$_3$C), 22.9 (C($\underline{C}$H$_3$)$_3$), 20.0 ($\underline{C}$H$_3$) *Minor isomer (R)* δ 173.3 ($\underline{C}$OOCH$_3$), 159.0 (Ar), 134.8 (H$\underline{C}$=CH_2), 130.6 (Ar), 128.9

(Ar), 118.0 (HC=$\underline{C}H_2$), 113.6 (Ar), 82.9 (Me$\underline{C}$OPMB), 66.3 ($\underline{C}H_2$-O), 63.0 ($\underline{C}$H-NH), 56.2 ($\underline{C}(CH_3)_3$), 55.2 (O$\underline{C}H_3$), 51.8 (COO$\underline{C}H_3$), 35.8 ($\underline{C}H_3C$), 22.6 (C($\underline{C}H_3)_3$), 19.1 ($\underline{C}H_3$).

FAB (+) HRMS: Calcd. for $C_{20}H_{31}NNaO_5S$: $(M+Na)^+$: *m/e* 420.18205; Found: *m/e* 420.18129.

Alcohol 403



To alkene **382** (180 mg, 0.453 mmol) in dry THF (2.26 mL) was added a BH_3-THF solution (1 M in THF, 0.22 mL, 0.226 mmol) at rt under N_2 . The resulting solution was stirred at rt for 1.5 h and EtOH (0.9 mL), a pH 7 buffer solution (0.9 mL) and H_2O_2 (30% in water, 0.9 mL) were added. (The pH 7 buffer was made by dissolving 2 g of NaOH pellet in 1 L of water and by adding 6.8 g of KH_2PO_4) The mixture was stirred for 1.5 h at rt, quenched slowly at 0 °C with sat. aq. $Na_2S_2O_3$ (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by SiO_2 flash column chromatography (gradient elution 5:1 to 1:3 petrol:EtOAc) afforded alcohol **403** as a white foam (88 mg, 40 %, 2 steps).

$[\alpha]_D$ + 8.5° (*c* 1.01, CH_2Cl_2).

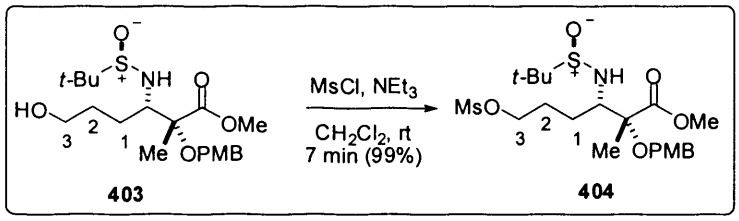
IR (neat film) 3333 (br), 2947 (s), 2908 (s), 2874 (s), 2837 (s), 1740 (s), 1612 (m), 1514 (s), 1460 (w), 1381 (w), 1300 (w), 1259 (s), 1202 (w), 1177 (w), 1117 (m), 1034 (m), 933 (w), 823.5 (w).

^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 7.27 (d, *J* = 8.7 Hz, 2 H, Ar), 6.84 (d, *J* = 8.7 Hz, 2 H, Ar), 4.57 (d, *J* = 10.3 Hz, 1 H, C$\underline{H}_2$-O), 4.40 (d, *J* = 10.3 Hz, 1 H, C$\underline{H}_2$-O), 3.89 (d, *J* = 8.5 Hz, 1 H, N$\underline{H}$), 3.76 (s, 3 H, OC$\underline{H}_3$), 3.74 (s, 3 H, COOC$\underline{H}_3$), 3.54 (m, 2 H, H3), 3.42 (td, *J* = 10.9, 2.6 Hz, 1 H, C$\underline{H}$-NH), 1.88 (s br, 1 H, O$\underline{H}$), 1.69 (m, 1 H, H1), 1.65 (s, 3 H, C$\underline{H}_3$), 1.63 (m, 1 H, H2), 1.44 (m, 2 H, H1, H2), 1.18 (s, 9 H, C(C$\underline{H}_3)_3$).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 173.7 (C$\underline{C}$OOCH$_3$), 159.2 (Ar), 130.4 (Ar), 129.3 (Ar), 113.7 (Ar), 82.5 (Me$\underline{C}$OPMB), 69.4 (C3), 66.6 ($\underline{C}$H$_2$-O), 62.8 ($\underline{C}$H-NH), 56.8 ($\underline{C}$(CH$_3$)$_3$), 55.2 (COOC$\underline{H}_3$), 52.2 (OC$\underline{H}_3$), 37.3 (CH$_3$-$\underline{C}$), 28.5 (C2), 26.0 (C1), 22.9 (C($\underline{C}$H$_3$)$_3$), 19.8 ($\underline{C}$H$_3$).

FAB (+) HRMS: Calcd. for $C_{20}H_{31}NnaO_6S$: $(M+Na)^+$: *m/e* 438.19262; Found: *m/e* 438.23181.

Mesylate 404



To a solution of alcohol **403** (460 mg, 1.11 mmol) in dry CH_2Cl_2 (3.7 mL) was added dropwise CH_3SO_2Cl (0.17 mL, 0.22 mmol) and NEt_3 (0.77 mL, 5.55 mL). The reaction mixture was stirred at rt for 7 min, quenched with water (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by SiO_2 flash column chromatography (gradient elution 3:1 to 1:2 petrol:EtOAc) afforded the title compound **404** as a colorless oil (540 mg, 99%).

$[\alpha]_D$ - 27.3° (*c* 0.67, CH_2Cl_2).

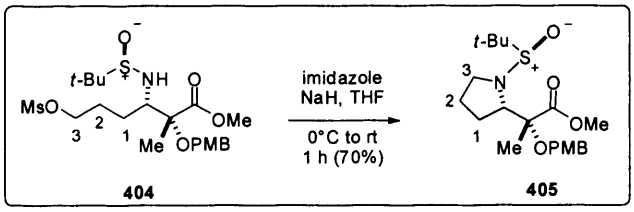
IR (neat film) 2963 (s), 1741 (m), 1612 (w), 1514 (w), 1454 (w), 1356 (m), 1259 (s), 1173 (m), 1101 (s), 1026 (s), 930 (w), 800 (s).

^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 7.27 (d, *J* = 8.7 Hz, 2 H, Ar), 6.84 (d, *J* = 8.7 Hz, 2 H, Ar), 4.59 (d, *J* = 10.3 Hz, 1 H, C$\underline{H}_2$-O), 4.40 (d, *J* = 10.3 Hz, 1 H, C$\underline{H}_2$-O), 4.13 (td, *J* = 6.07, 0.9 Hz, 2 H, H3), 3.86 (d, *J* = 8.4 Hz, 1 H, N$\underline{H}$), 3.77 (s, 3 H, OC$\underline{H}_3$), 3.76 (s, 3 H, OC$\underline{H}_3$), 3.43 (td, *J* = 9.3, 2.9 Hz, 1 H, C$\underline{H}$-NH), 2.93 (s, 3 H, C$\underline{H}_3$-S), 1.92 (m, 1 H, H2), 1.66 (s, 3 H,C$\underline{H}_3$), 1.63 (m, 2 H, H2, H1), 1.45 (m, 1 H, H1), 1.17 (s, 9 H, C(C$\underline{H}_3$)$_3$).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 173.9 (COO<u>C</u>H_3), 159.1 (Ar), 130.5 (Ar), 129.3 (Ar), 113.7 (Ar), 82.5 (Me<u>C</u>OPMB), 66.5 (<u>C</u>H_2-O), 63.2 (<u>C</u>H-NH), 62.1 (C3) 56.7 (<u>C</u>(CH_3)$_3$), 55.2 (COO<u>C</u>H_3), 52.1 (O<u>C</u>H_3), 29.5 (C1), 28.6 (C2), 22.9 (C(<u>C</u>H_3)$_3$), 19.7 (<u>C</u>H_3).

FAB (+) HRMS: Calcd. for $C_{21}H_{35}NNaO_8S$: $(M+H)^+$: *m/e* 494.18822; Found: *m/e* 494.18907.

Ester 405



To mesylate **404** (367 mg, 0.743 mmol) in THF (2.5 mL) at 0 °C under N_2 was added imidazole (5 mg, 0.074 mmol) followed by NaH (60% dispersion in oil, 60 mg, 1.490 mmol). The reaction mixture was stirred at 0 °C for 15 min and at rt for a further 1 h. The reaction mixture was quenched with MeOH (0.3 mL) and water (2 mL) and extracted with Et_2O (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by SiO_2 flash column chromatography (gradient elution 3:1 to 1:1 petrol:EtOAc) afforded the title compound **405** as a yellow oil (227 mg, 70%).

$[\alpha]_D$ + 38.6° (*c* 0.74, CH_2Cl_2).

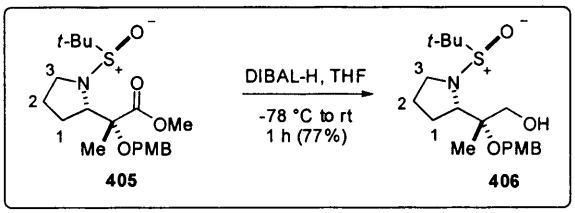
IR (neat film) 3442 (s), 2953 (s), 1738 (s), 1612 (w), 1514 (m), 1456 (m), 1383 (w), 1250 (s), 1173 (w), 1120 (m), 1078 (w), 1034 (w), 822 (w).

^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 7.30 (d, *J* = 8.5 Hz, 2 H, Ar), 6.81 (d, *J* = 8.6 Hz, 2 H, Ar), 4.36 (s, 2 H, C<u>H</u>$_2$-O), 4.03 (dd, *J* = 8.0, 2.7 Hz, 1 H, C<u>H</u>-N), 3.74 (s, 3 H, OC<u>H</u>$_3$), 3.71 (s, 3 H, OC<u>H</u>$_3$), 3.28 (m, 1 H, H3), 3.16 (m, 1 H, H3), 2.01 (m, 1 H, H2), 1.76 (m, 2 H, H2, H1), 1.68 (m, 1 H, H1), 1.56 (s, 3 H, C<u>H</u>$_3$C), 1.15 (s, 9 H, C(C<u>H</u>$_3$)$_3$).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 173.9 (COO<u>C</u>H_3), 158.8 (Ar), 130.7 (Ar), 128.9 (Ar), 113.5 (Ar), 83.4 (Me<u>C</u>OPMB), 66.3 (<u>C</u>H_2-O), 64.7 (<u>C</u>H-NH), 58.4 (<u>C</u>(CH_3)$_3$), 55.1 (COO<u>C</u>H_3), 52.0 (O<u>C</u>H_3), 50.2 (C3), 29.5 (C2), 28.6 (C1), 23.2 (C(<u>C</u>H_3)$_3$), 18.5 (<u>C</u>H_3).

FAB (+) HRMS: Calcd. for $C_{17}H_{25}NNaO_5S$: $(M+Na)^+$: *m/e* 368.18954; Found: *m/e* 368.19047.

Alcohol 406



To ester **405** (255 mg, 0.641 mmol) in THF (2.2 mL) at -78 °C under N_2 was added dropwise a solution of DIBAL-H (1.5 M in toluene, 0.94 mL, 1.28 mmol).[104] The reaction mixture was stirred at -78 °C for 10 min and at rt for 1 h. A saturated aqueous solution of Rochelle's salt (5 mL) was added followed by Et_2O (10 mL). The mixture was stirred at rt for 1 h and extracted with Et_2O (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by SiO_2 flash column chromatography (gradient elution 4:1 to 1:1 petrol:EtOAc) afforded alcohol **406** as a white foam (212 mg, 89%).

$[\alpha]_D$ + 46.7° (*c* 0.51, CH_2Cl_2).

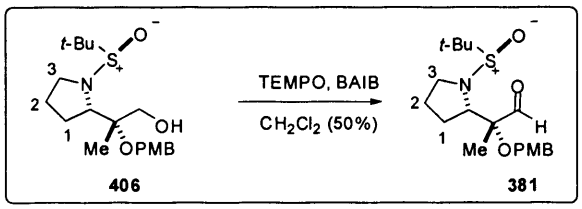
IR (neat film) 3391 (br), 2957 (s), 2874 (m), 2874 (s), 1612 (w), 1514 (s), 1462 (m), 1371 (w), 1300 (w), 1246 (s), 1173 (w), 1121 (w), 1070 (s), 1040 (s), 822 (w).

^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 7.25 (d, *J* = 8.7 Hz, 2 H, Ar), 6.82 (d, *J* = 8.7 Hz, 2 H, Ar), 4.53 (d, *J* = 10.8 Hz, 1 H, C<u>H</u>$_2$-OAr), 4.49 (d, *J* = 10.8 Hz, 1 H, C<u>H</u>$_2$-O), 4.19 (dd, *J* = 8.4, 5.7 Hz, 1 H, C<u>H</u>-N), 3.80 (dd, *J* = 12.8 Hz, 1 H, C<u>H</u>$_2$OH), 3.75 (s, 3 H, OC<u>H</u>$_3$), 3.66 (dd, *J* = 12.8, 9.0 Hz, 1 H, C<u>H</u>$_2$OH), 3.11 (m, 1 H, H3), 3.04 (m, 1 H, H3), 1.95 (m, 2 H, H1), 1.83 (m, 1 H, H2), 1.70 (m, 1 H, H2), 1.15 (s, 9 H, C(C<u>H</u>$_3$)$_3$), 1.06 (s, 3 H, C<u>H</u>$_3$).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 158.7 (Ar), 131.5 (Ar), 128.8 (Ar), 113.5 (Ar), 80.2 (Me<u>C</u>OPMB), 64.5 (<u>C</u>H_2-OH), 64.1 (<u>C</u>H_2-OAr), 60.1 (<u>C</u>HN), 58.7 (<u>C</u>$(CH_3)_3$), 55.2 (O<u>C</u>H_3), 51.2 (C3), 26.5 (C1), 25.7 (C2), 22.9 (C(<u>C</u>H_3)$_3$), 16.7 (<u>C</u>H_3).

FAB (+) HRMS: Calcd. for $C_{19}H_{31}NNaO_4S$: $(M+Na)^+$: *m/e* 393.19496; Found: *m/e* 393.19392.

Aldehyde 381



To a solution of alcohol **406** (0.10 g, 0.271 mmol) in dry CH_2Cl_2 (2.7 mL) at rt under N_2 was added TEMPO (6.8 mg, 0.044 mmol) followed by [bis(acetoxy)iodo]benzene (141 mg, 0.439 mmol). The reaction mixture was stirred at rt for 5 h, quenched with sat. aq. $Na_2S_2O_3$ (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by SiO_2 flash chromatography (gradient elution: 5:1 to 1:1 petrol:EtOAc) to afford aldehyde **381** as a colorless oil (50 mg, 50%).[104]

$[\alpha]_D$ + 39.4° (*c* 0.45, CH_2Cl_2).

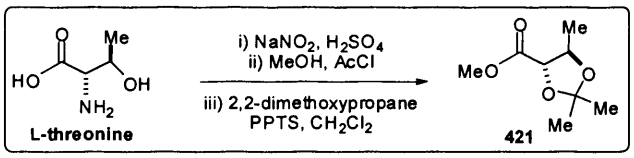
IR (neat film) 2956 (s), 1730 (s), 1612 (w), 1514 (s), 1462 (m), 1385 (w), 1362 (w), 1302 (w), 1248 (s), 1175 (w), 1127 (w), 1088 (s), 1034 (s), 822 (w).

^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 9.68 (s, 1 H, C<u>H</u>O), 7.24 (d, *J* = 8.7 Hz, 2 H, Ar), 6.84 (d, *J* = 8.7 Hz, 2 H, Ar), 4.46 (d, *J* = 10.8 Hz, 1 H, C<u>H</u>$_2$-O), 4.28 (d, *J* = 10.8 Hz, 1H, C<u>H</u>$_2$-O), 4.06 (t, *J* = 6.7 Hz, 1 H, C<u>H</u>-N), 3.78 (s, 3 H, OC<u>H</u>$_3$), 3.19 (m, 1 H, H3), 3.11 (m, 1 H, H3), 1.89 (m, 2 H, H1), 1.72 (m, 2 H, H2), 1.37 (s, 3 H, C<u>H</u>$_3$), 1.13 (s, 9 H, C(C<u>H</u>$_3$)$_3$).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 204.1 (C=O), 159.2 (Ar), 130.2 (Ar), 129.2 (Ar), 113.7 (Ar), 84.5 (MeCOPMB), 66.1 (CH_2-O), 62.2 (CH-NH), 58.5 ($C(CH_3)_3$), 55.2 (OCH_3), 51.3 (C3), 29.7 (C1), 27.1 (C2), 24.9 ($C(CH_3)_3$), 14.1 (CH_3).

FAB (+) HRMS: Calcd. for $C_{19}H_{30}NO_4S$: $(M+H)^+$: *m/e* 368.18954; Found: *m/e* 368.19047.

Ester 421



(L)-Threonine (110 g, 0.92 mol) was suspended in water (250 mL) at -5 °C and was treated simultaneously while stirring with a solution of $NaNO_2$ (69 g, 1 mol) in water (100 mL) and concentrated H_2SO_4 (27.9 mL, 0.5 mol) in water (75 mL). The two solutions were added at such a rate that the temperature remained between 0 °C and 5 °C. The solution was then stirred at rt for 20 h. The water was evaporated *in vacuo* and the remaining mixture treated with EtOH (150 mL). The salts were then filtered and the solution evaporated to dryness. The crude mixture was dissolved in MeOH (150 mL) and acetyl chloride (128 mL, 1.4 mol) was added very slowly at 0 °C under N_2. The reaction mixture was then refluxed for 6 h. Evaporation of the solvent gave the crude dihydroxy ester which was dissolved in CH_2Cl_2 (150 mL) and treated with 2,2-dimethoxypropane (226 mL, 1.84 mol) and PPTS (23 g, 0.092 mol). The reaction mixture was stirred at rt for 20 h, quenched with aq. sat. $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 150 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Distillation (70-75 °C, 1 mmHg) afforded methyl ester **421** (70 g, 43%) as a colorless oil.[108]

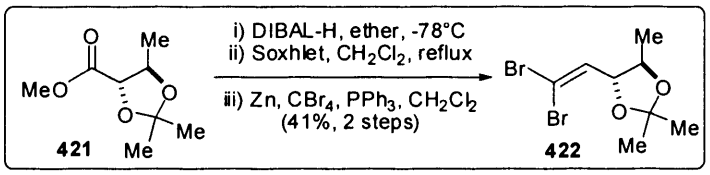
$[\alpha]_D$ - 17.1° (*c* 1, $CHCl_3$).

^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 4.01 (dq, *J* = 8.0, 6.0 Hz, 1 H, CH-CH_3), 3.87 (d, *J* = 8.0 Hz, 1 H, CH-C=O), 3.60 (s, 3 H, O-CH_3), 1.37 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3)

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 170.8 (C=O), 110.5 ($C(CH_3)_2$), 80.3 (CH-C=O), 75.0 (CH-CH_3), 52.3 (O-CH_3), 27.1 ($C(CH_3)_2$), 25.6 ($C(CH_3)_2$), 18.4 (CH-CH_3).

The spectral data for this molecule corresponded with that in the literature.

Dibromide 422



To a solution of the ester **421** (15 g, 83.1 mmol) in dry ether (90 mL) at -78 °C was added dropwise over 30 min via addition funnel, a solution of DIBAL-H in hexanes (1 M, 100 mL, 100 mmol). The reaction mixture was stirred at -78 °C for 45 min and quenched with a saturated aqueous solution of Rochelle's salt (100 mL). The mixture was poured into a conical flask containing Et_2O (200 mL), stirred at rt for 1 h and extracted with Et_2O (3 x 250 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a mixture of the aldehyde and its hydrate. The crude oil was dissolved in CH_2Cl_2 (120 mL) and the mixture was heated at reflux for 20 h in a Soxhlet apparatus containing activated 4 Å powdered molecular sieves. The reaction mixture was directly added to a suspension which has been prepared as follows. To a suspension of CBr_4 (55.0 g, 166 mmol) and Zn (10.85 g, 166 mmol) at 0 °C in CH_2Cl_2 (320 mL) was added PPh_3 by portions ove 20 min (43.50 g, 166 mmol). After 24 h at rt, the crude aldehyde in CH_2Cl_2 was added *via* canula over 10 min at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and then poured onto petrol (200 mL) and filtered through Celite®. The filtrate was concentrated in *vacuo*, the residue was filtered through Celite® and the Celite® was washed with petroleum ether (5 x 100 mL). The procedure was repeated until no dibromoolefin was detected by TLC. The crude oil was purified by SiO_2 flash chromatography (20:1 petrol:EtOAc) to afford the desired unstable product **422** as a colorless oil (10.3 g, 41% over 2 steps).[109]

$[\alpha]_D$ - 3.1° (*c* 1, $CHCl_3$).

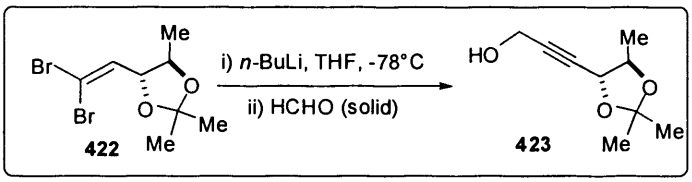
IR (neat film) 3460 (br, w), 2984 (s), 2934 (m), 2874 (m), 1622 (m), 1452 (m), 1377 (s), 1242 (s), 1173 (s), 1092 (s), 1038 (s), 926 (m), 862 (s), 810 (m), 783 (s).

^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 6.42 (d, *J* = 7.9 Hz, 1 H, Br_2C=CH), 4.21 (t, *J* = 8.3 Hz, 1 H, OC<u>H</u>C=), 3.86 (m, 1 H, OC<u>H</u>CH_3), 1.80 (br, O<u>H</u>), 1.43 (s, 3 H, CC<u>H</u>$_3$), 1.37 (s, 3 H, CC<u>H</u>$_3$), 1.32 (d, *J* = 6.2 Hz, 3 H, CHC<u>H</u>$_3$).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 135.4 (Br_2C=<u>C</u>H), 109.3.0 (<u>C</u>$(CH_3)_2$), 93.8 (Br_2<u>C</u>=), 82.1 (O<u>C</u>HC=), 75.8 (O<u>C</u>HCH_3), 27.2 (C<u>C</u>H_3), 26.7 (C<u>C</u>H_3), 17.0 (CH<u>C</u>H_3).

The spectral data for this molecule corresponded to those reported in the literature.

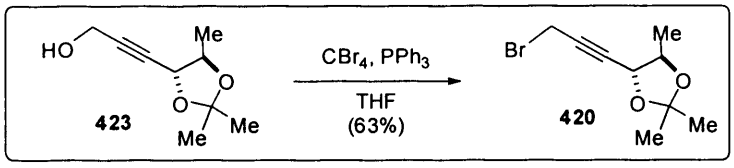
Alcohol 423



To a solution of the dibromo olefin **422** (5.4 g, 18.1 mmol) in dry THF (80 mL) at -78 °C under N_2 was added dropwise over 5 min a solution of *n*-BuLi (2.5 M in hexanes, 16 mL, 39.9 mmol). The reaction mixture was stirred at -78 °C for 1 h and then allowed to warm to rt where it was stirred for a further 1.5 h before being cooled to -78 °C. Solid paraformaldehyde (1.0 g, 36.2 mmol) was added in one portion and the reaction was held at -78 °C for 30 min before being warmed to rt where it was stirred for 1 h. Brine (100 mL) was added to the reaction mixture which was then extracted with Et_2O (3 x 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was quickly purified by SiO_2 flash chromatography (gradient elution: 10:1 to 3:1 petrol:EtOAc) to afford the propargylic alcohol **423** as a non stable colorless oil (2.83 g, 92%). The structure of alcohol **423** was confirmed by its 500 MHz ^{1}H-NMR spectrum in $CDCl_3$ and was used directly without further characterisation.

^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 4.29 (s br, 2 H, CH_2OH), 4.15 (dt, *J* = 8.2, 1.6 Hz, 1 H, OC<u>H</u>CΞC), 4.06 (ddd, *J* = 11.9, 8.2, 6.0 Hz, 1 H, OC<u>H</u>CH_3), 1.80 (br, O<u>H</u>), 1.42 (s, 3 H, CC<u>H</u>$_3$), 1.39 (s, 3 H, CC<u>H</u>$_3$), 1.32 (d, *J* = 6.0 Hz, 3 H, CHC<u>H</u>$_3$) .

Bromide 420

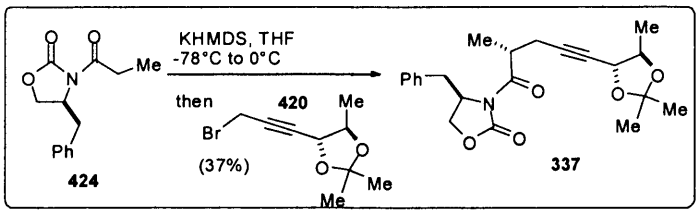


To the propargylic alcohol **423** (4.1g, 24 mmol) and PPh_3 (12.6 g, 48 mmol) in dry THF (120 mL) at 0 °C was added by portions over 30 min, CBr_4 (16 g, 48 mmol). The resulting brown mixture was stirred at 0 °C for 20 min and petrol (100 mL) and ether (100 mL) were added. Triphenylphosphine oxide was removed by filtration through Celite® and the filtered pad washed with petrol (3 x 150 mL). The procedure was repeated until no bromide was detected by TLC. The filtrate and washings were concentrated *in vacuo*. The crude oil was quickly purified by SiO_2 flash chromatography (gradient elution 40:1 to 20:1 petrol:EtOAc) to afford **420** as an unstable yellow oil (3.5 g, 63%).

The structure of **420** was confirmed by its 500 MHz ^{1}H-NMR spectrum in $CDCl_3$ and was used directly without further characterisation.

^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 4.15 (dt, *J* = 8.2, 1.9 Hz, 1 H, OC<u>H</u>CΞC), 4.05 (ddd, *J* = 11.9, 8.2, 6.0 Hz, 1 H, OC<u>H</u>CH_3), 4.29 (d, *J* = 1.8 Hz, 2 H, C<u>H</u>$_2$Br), 1.42 (s, 3 H, CC<u>H</u>$_3$), 1.40 (s, 3 H, CC<u>H</u>$_3$), 1.30 (d, *J* = 6.0 Hz, 3 H, CHC<u>H</u>$_3$).

Alkyne 337



To a solution of **424** (0.91 g, 3.90 mmol) in THF (8 mL) at -78 °C under N_2 was added dropwise over 10 min a solution of KHMDS (0.5 M in PhMe, 9.36 mL, 4.68 mmol). The reaction mixture was stirred at -78 °C for 1 h. A solution of bromide **420** (0. 91 g, 3.90 mmol) in THF (10 mL) was added dropwise over 10 min *via* canula. The reaction mixture was stirred at -78 °C for 40 min and at 0 °C for 2 h. The mixture was then quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by SiO_2 flash chromatography; gradient elution: 20:1 to 6:1 petrol:EtOAc to recover the unreacted starting material **424** (0.2 g, 22%) and 5:1 to 4:1 to afford alkyne **337** in the form of a colorless oil (0.685 g, 45%).

$[\alpha]_D$ + 30.2° (*c* 0.45, CH_2Cl_2).

IR (neat film) 2982 (w), 2922 (m), 2852 (w) 1780 (s),1699 (m), 1454 (w), 1385 (m), 1242 (m), 1213 (m), 1171 (w), 1094 (m), 1028 (m).

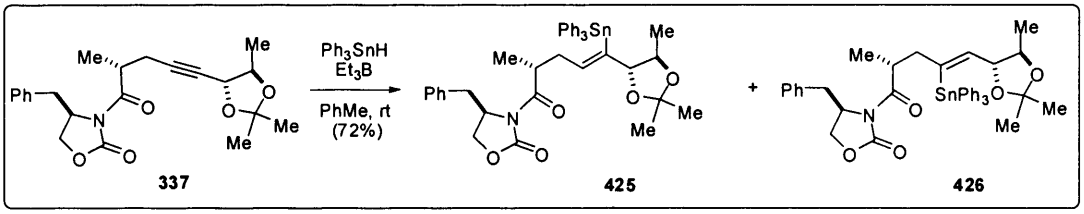
^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 7.35-7.26 (m, 5 H, Ar), 4.66 (m, 1 H, C<u>H</u>-N), 4.17 (dd, *J* = 16.7, 9.0 Hz, 1 H, C<u>H</u>$_2$O), 4.14 (dd, *J* = 9.0, 3.2 Hz, 1 H, C<u>H</u>$_2$O), 4.09 (dt, *J* = 8.1, 1.9 Hz, 1 H, CΞC-C<u>H</u>-O), 3.99 (qd, *J* = 8.1, 6.0 Hz, 1 H, CH$_3$-C<u>H</u>-O), 3.91 (m, 1H, CH$_2$-C<u>H</u>-CH$_3$), 3.27 (dd, *J* = 13.4, 3.3 Hz, 1 H, C<u>H</u>$_2$Ar), 2.74 (dd, *J* = 13.4, 9.5 Hz, 1 H, C<u>H</u>$_2$Ar), 2.61 (ddd, *J* = 16.9, 6.9, 2.0 Hz, 1H, CH-C<u>H</u>$_2$-CΞ), 2.53 (ddd, *J* = 16.9, 6.9, 2.0 Hz, 1 H, CH-C<u>H</u>$_2$-CΞ), 1.35 (s, 3 H, CC<u>H</u>$_3$), 1.34 (s, 3 H, CC<u>H</u>$_3$), 1.28 (d, *J* = 6.0 Hz, 3 H, C<u>H</u>$_3$CHO), 1.19 (d, *J* = 6.9 Hz, 3 H, C<u>H</u>$_3$CH).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 174.9 (CH<u>C</u>=O), 152.9 (O-<u>C</u>=O), 135.1(C, Ar), 129.3 (CH, Ar), 128.9 (CH, Ar), 127.3 (C, Ar), 109.2 (<u>C</u>(CH$_3$)$_2$), 84.1 (CH$_2$-<u>C</u>ΞC), 77.9 (CΞ<u>C</u>-CHO), 77.5

(CH_3-CH-O), 72.1 (C≡C-CH-O), 66.1 (CH_2O), 55.2 (CH-N), 37.9 (CH_2Ar), 37.2 (CH_2CHCH_3), 27.1 ($C(CH_3)_2$), 26.3 ($C(CH_3)_2$), 16.8 (CH_3CHO), 16.5 (CH_3CH).

FAB (+) HRMS: Calcd. for $C_{22}H_{27}NNaO_5$: $(M+Na)^+$: *m/e* 408.17868; Found: *m/e* 408.178770.

Stannane 425



Ph_3SnH (0.418 g, 1.19 mmol) was weighed in a glove bag and added to a round-bottomed flask containing alkyne **337** (0.230 g, 0.596 mmol). The flask was immediately purged with N_2 and dry PhMe (0.6 mL) was added. Et_3B (1 M solutions in hexanes, 0.21 mL, 0.21 mmol) was then added dropwise. Air was injected into the reaction vessel to initiate the reaction. The reactants were stirred at rt overnight. H_2O (10 mL) was added and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by SiO_2 flash chromatography (gradient elution: 100:1 to 25:1 petrol:EtOAc) without separation of the individual vinylstannanes **425** and **426** from each other. 500 MHz NMR analysis of this unseparated mixture in $CDCl_3$ indicated that vinylstannanes **425** and **426** were present in 10:1 ratio. The mixture was obtained in the form of a colorless oil (0.33 g, 75%).[105] The structure of the minor isomer **426** is only assigned tentatively.

$[\alpha]_D$ + 15.1° (*c* 0.33, CH_2Cl_2).

IR (neat film) 3061 (w), 2980 (m), 2928 (m), 2862 (w), 1780 (s), 1699 (m), 1614 (w), 1429 (m), 1383 (s), 1213 (s), 1097 (m), 1024 (m), 972 (w), 918 (w), 731 (m), 700.1 (m), 509 (w), 451 (w).

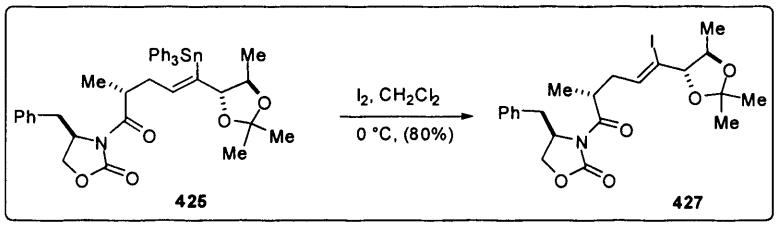
^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 7.64-7.13 (m, 20 H, Ar), 6.60 (dd, *J* = 6.62, 8.20 Hz (^3J ^{117}Sn-^{1}H = 149 Hz), 1 H, HC=CSn), 4.54 (m, 1 H, CH-N), 4.10 (dd, *J* = 9.0 Hz, 1 H, CH_2O), 4.07

(ddd, J = 9.0, 3.1 Hz, 1 H, C$\underline{H}_2$O), 3.75 (m, CH_3-C$\underline{H}$-O), 3.62 (m, CH_3-C$\underline{H}$-C=O), 3.12 (dd, J = 13.4, 3.3 Hz, 1 H, C$\underline{H}_2$Ar), 2.74 (dd, J = 13.4, 9.5 Hz, 1 H, C$\underline{H}_2$Ar), 2.61 (m, 1 H, C$\underline{H}_2$CH=), 2.17 (m, 1 H, C$\underline{H}_2$CH=), 1.25 (s, 3 H, CC$\underline{H}_3$), 1.20 (d, J = 6.1 Hz, 3 H, C$\underline{H}_3$CH-O), 0.79 (d, J = 6.9 Hz, 3 H, C$\underline{H}_3$CHC=O), 0.66 (s, 3 H, CC$\underline{H}_3$).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 176.0 (CH$\underline{C}$=O), 152.9 (O-$\underline{C}$=O), 144.3 (H$\underline{C}$=CSn), 140.1, 139.7 ($\underline{C}$Sn), 137.1 129.5, 129.3, 129.1, 128.9, 128.8, 128.5, 128.3, 127.3, 107.9 ($\underline{C}(CH_3)_2$), 89.3 ($\underline{C}$HN), 65.9 ($\underline{C}H_2$-O), 55.3 ($\underline{C}$H-N), 38.0 ($\underline{C}H_2$Ar), 37.6 ($CH_3\underline{C}$HC=O), 37.4 ($\underline{C}H_2$CH=) 27.2 (C($\underline{C}H_3)_2$), 25.9 (C($\underline{C}H_3)_2$, 16.7 ($\underline{C}H_3$CHO), 16.4 ($\underline{C}H_3$CHC=O).

FAB (+) HRMS: Calcd. for $C_{40}H_{43}NNaO_5Sn$: $(M+Na)^+$: *m/e* 760.20608; Found: *m/e* 760.20449.

Iodide 427



To a stirred solution of vinyl triphenylstannane **425** (250 mg, 0.338 mmol) in dry CH_2Cl_2 (4 mL)at 0 °C under N_2 was added solid I_2 (103 mg, 0.406 mmol) in one portion. The mixture was stirred at rt for 1 h. The solvent was removed in vacuo and the residue purified by SiO_2 flash chromatography (gradient elution: 20:1 to 6:1 petrol:EtOAc) to give vinyl iodide **427** as a pale yellow oil (140 mg, 80%).[107]

$[\alpha]_D$ + 41.8° (*c* 0.16, CH_2Cl_2).

IR (neat film) 2982 (m), 2930 (m), 2851 (w) 1780 (s), 1724 (m), 1699 (m), 1454 (w), 1383 (m), 1350 (w), 1242 (s), 1211 (m), 1175 (w), 1099 (m), 1036 (m), 974 (w), 858 (w), 731 (m), 702 (m).

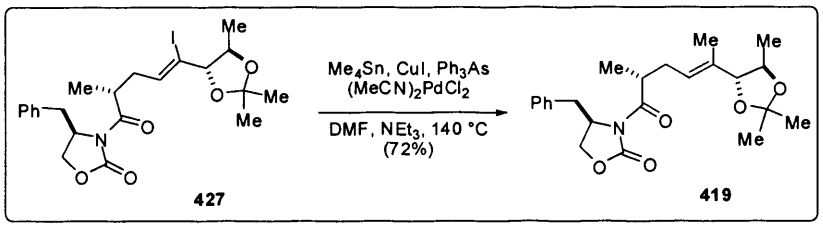
^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 7.34-7.17 (m, 5 H, Ar), 6.14 (t, J = 6.8 Hz, 1 H, $\underline{H}$C=Cl), 4.66 (m, 1 H, C$\underline{H}$-N), 4.18 (dd, J = 16.5, 9.1 Hz, 1 H, C$\underline{H}_2$O), 4.15 (dd, J = 9.1, 3.1 Hz, 1 H,

C$\underline{H}_2$O), 4.0 (qd, J = 8.0, 6.0 Hz, 1 H, CH_3-C$\underline{H}$-O), 3.90 (m, 1 H, CH_3-C$\underline{H}$-C=O) 3.59 (d, J = 8.0 Hz, 1 H, IC-C$\underline{H}$-O), 3.27 (dd, J = 13.4, 3.1 Hz, 1 H, C$\underline{H}_2$Ar), 2.77 (dd, J = 13.4, 9.9 Hz, 1 H, C$\underline{H}_2$Ar), 2.63 (m, 1 H, CH-C$\underline{H}_2$-CH=C), 2.54 (m, 1 H, CH-C$\underline{H}_2$-CH=C), 1.48 (s, 3 H, C(C$\underline{H}_3$)$_2$), 1.41 (s, 3 H, C(C$\underline{H}_3$)$_2$), 1.28 (d, J = 6.1 Hz, 3 H, C$\underline{H}_3$CHO), 1.19 (d, J = 6.8 Hz, 3 H, C$\underline{H}_3$CH).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 175.8 (CH$\underline{C}$=O), 153.1 (O-$\underline{C}$=O), 136.4 (H$\underline{C}$=Cl), 135.2 (Ar), 129.4 (Ar), 129.0 (Ar), 127.4 (Ar), 109.1 ($\underline{C}$(CH$_3$)$_2$), 109.0 (HC=$\underline{C}$l), 87.8 (IC-$\underline{C}$H-O), 77.6 (CH_3-$\underline{C}$H-O), 66.1 ($\underline{C}H_2O$), 55.4 ($\underline{C}$H-N), 39.6 (CH-$\underline{C}H_2$-CH=C), 38.1 ($\underline{C}H_2$Ar), 36.8 (CH_3-$\underline{C}$H-CH_2), 27.7 (C($\underline{C}H_3$)$_2$), 27.1 (C($\underline{C}H_3$)$_2$, 16.8 ($\underline{C}H_3$CHO), 16.4 ($\underline{C}H_3$CH).

FAB (+) HRMS: Calcd. for $C_{22}H_{28}INNaO_5$: $(M+Na)^+$: *m/e* 536.09044; Found: *m/e* 536.09098.

Alkene 419



To a solution of vinyl iodide **427** (57 mg, 0.11 mmol) in dry DMF (1.1 mL) and freshly distilled Et_3N (1.1 mL, 7.89 mmol) at rt under N_2 was added Me_4Sn (0.05 mL, 0.36 mmol), CuI (2 mg, 0.011 mmol), and Ph_3As (3.3 mg, 0.011 mmol) followed by $(MeCN)_2PdCl_2$ (2.8 mg, 0.011 mmol). The reactants were heated at 130 °C for 2 h, cooled to rt, and H_2O (5 mL) was added. After extraction with Et_2O (3 x 5 mL), the combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by SiO_2 flash chromatography (gradient elution: 100:1 to 6:1 petrol:EtOAc) to afford alkene **419** in the form of a colorless oil (32 mg, 72%).[107]

$[\alpha]_D$ + 4.4° (*c* 0.20, CH_2Cl_2).

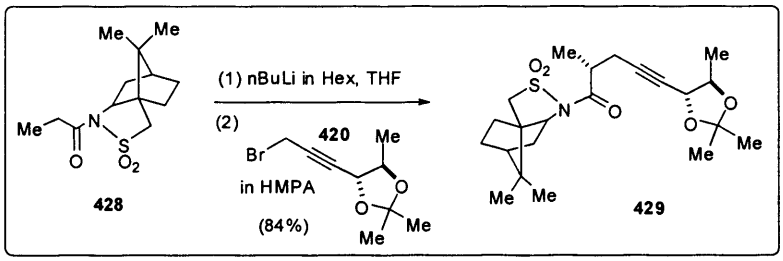
IR (neat film) 2980 (m), 2926 (m), 2876 (w) 1780 (s), 1724 (m), 1452 (w), 1383 (m), 1242 (s), 1097 (m), 1036 (w), 974 (w), 729 (m).

^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 7.35-7.15 (m, 5 H, Ar), 5.53 (t, *J* = 7.2 Hz, 1 H, H$\underline{C}$=CCH$_3$), 4.66 (m, 1 H, C$\underline{H}$-N), 4.15 (dd, *J* = 16.5, 9.1 Hz, 1 H, C$\underline{H_2}$O), 4.15 (dd, *J* = 9.1, 3.1 Hz, 1 H, C$\underline{H_2}$O), 3.83 (m, 3 H, CH$_3$-C$\underline{H}$-O, CH$_3$-C$\underline{H}$-CH$_2$, IC-C$\underline{H}$-O), 3.26 (dd, *J* = 13.4, 3.4 Hz, 1 H, C$\underline{H_2}$Ar), 2.69 (dd, *J* = 13.4, 9.9 Hz, 1 H, C$\underline{H_2}$Ar), 2.50 (m, 1 H, CH-C$\underline{H_2}$-CH=), 2.27 (m, 1 H, CH-C$\underline{H_2}$-CH=), 1.67 (s, 3 H, =C(C$\underline{H_3}$)), 1.38 (s, 3 H, C(C$\underline{H_3}$)$_2$), 1.37 (s, 3 H, C(C$\underline{H_3}$)$_2$), 1.20 (d, *J* = 5.6 Hz, 3 H, C$\underline{H_3}$CHO), 1.15 (d, *J* = 6.8 Hz, 3 H, C$\underline{H_3}$CH).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 176.6 (CH$\underline{C}$=O), 153.1 (O-$\underline{C}$=O), 135.3 (Ar), 127.3 (Ar), 126.3 (H$\underline{C}$=CCH$_3$), 108.0 ($\underline{C}$(CH$_3$)$_2$), 109.0 (HC=$\underline{C}$l), 88.4 (CH$_3$C-$\underline{C}$H-O), 74.4 (CH$_3$-$\underline{C}$H-O), 66.0 ($\underline{C}$H$_2$O), 55.4 ($\underline{C}$H-N), 38.0 ($\underline{C}$H$_2$Ar), 37.4 (CH$_2\underline{C}$HCH$_3$), 31.9 (CH-$\underline{C}$H$_2$-CH=), 27.5 (C($\underline{C}$H$_3$)$_2$), 26.9 (C($\underline{C}$H$_3$)$_2$, 17.0 ($\underline{C}$H$_3$CHO), 16.4 (C=C$\underline{C}$H$_3$).

FAB (+) HRMS: Calcd. for $C_{23}H_{31}NNaO_5$: $(M+Na)^+$: *m/e* 424.20998; Found: *m/e* 424.21073.

Alkyne 429



To a solution of compound **428**[111] (1.16 g, 4.29 mmol) in THF (21 mL) at -78 °C under N_2 was added dropwise over 10 min a solution of *n*-BuLi (2.5 M in Hexanes, 1.7 mL, 4.29 mmol). The reaction mixture was stirred at -78 °C for 1 h and a solution of bromide **420** (1.0 g, 4.3 mmol) in HMPA (2.24 mL, 12.9 mmol) was added dropwise *via* canula over 10 min. The reaction mixture was stirred at -78 °C for 4 h, quenched with water (20 mL) and extracted with Et_2O (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by SiO_2 flash chromatography (gradient elution: 50:1 to 20:1 petrol:EtOAc) to afford alkyne **429** in the form of a white foam (1.53 g, 84%).

$[\alpha]_D$ + 52.2° (*c* 1, CH_2Cl_2).

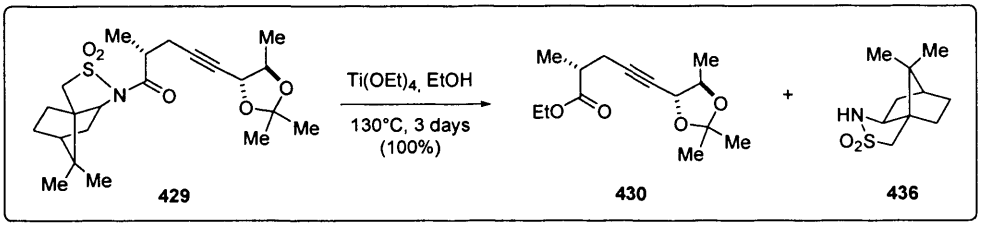
IR (neat film) 2980 (s), 2887 (m), 1697 (s), 1456 (w), 1381 (m), 1331 (s), 1267 (m), 1236 (s), 1169 (m), 1128 (m), 1093 (w), 1061 (w), 1030 (m), 976 (w), 860 (w), 769 (w), 540 (m).

^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 4.03 (dt, *J* = 8.3, 1.8 Hz, 1 H, CΞC-C<u>H</u>-O), 3.96 (qd, *J* = 8.1, 5.9 Hz, 1 H, CH_3-C<u>H</u>-O), 3.85 (dd, *J* = 7.5, 5.0 Hz, 1 H, C<u>H</u>-N), 3.44 (q, *J* = 13.8 Hz , 2H, O_2S-C<u>H_2</u>), 3.25 (m, 1 H, C<u>H</u>-CH_3), 2.55 (ddd, *J* = 16.6, 6.4, 1.8 Hz, 1 H, CH-C<u>H_2</u>-CΞ), 2.49 (ddd, *J* = 16.6, 6.4, 1.8 Hz, 1 H, CH-C<u>H_2</u>-CΞ), 2.04 (m, 2 H, C<u>H_2</u>-CHN), 1.85 (m, 3 H, CH_2-CH-C<u>H_2</u>, C<u>H</u>C(CH_3)$_2$), 1.38 (s, 3 H, $O_2C(CH_3)_2$), 1.36 (m, 2 H, CC<u>H_2</u>-CH_2) 1.35 (s, 3 H, $O_2C(CH_3)_2$, 1.27 (d, *J* = 6.0 Hz, 3 H, C<u>H_3</u>CHO), 1.19 (d, *J* = 6.6 Hz, 3 H, C<u>H_3</u>CH), 1.14 (s, 3 H, HCC(C<u>H_3</u>)$_2$), 0.94 (s, 3 H, HCC(C<u>H_3</u>)$_2$).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 174.0 (<u>C</u>=O), 109.1 (<u>C</u>(CH_3)$_2$), 83.6 (CH_2-<u>C</u>ΞC), 78.1 (CΞ<u>C</u>-CHO), 77.5 (CH_3-<u>C</u>H-O), 72.0 (CΞC-<u>C</u>H-O), 65.2 (<u>C</u>H-N), 53.1 (<u>C</u>H_2-S), 48.3 (<u>C</u>CH_3 (X_C)), 47.7 (<u>C</u>-CH_2S), 44.6 (<u>C</u>HC(CH_3)$_2$), 39.0 (<u>C</u>H-CH_3), 38.4 (<u>C</u>H_2-CHN), 32.8 (<u>C</u>H_2), 27.1 ($O_2C(\underline{C}H_3)_2$), 26.4 (CH_2-<u>C</u>H_2), 26.4 (HC(<u>C</u>H_3)$_2$), 24.3 (CH-<u>C</u>H_2-CΞC), 20.9 (HC(<u>C</u>H_3)$_2$), 19.8 ($O_2C(\underline{C}H_3)_2$), 16.6 (<u>C</u>H_3CHO), 16.0 (<u>C</u>H_3CH).

FAB (+) HRMS: Calcd. for $C_{22}H_{33}NNaO_5S$: $(M+Na)^+$: *m/e* 446.19770; Found: *m/e* 446.19707.

Alkyne 430



To a solution of alkyne **429** (760 mg, 1.8 mmol) in absolute EtOH (36 mL) was added $Ti(OEt)_4$ (3.77 mL, 18 mmol) in one portion. The resulting heterogeneous mixture was heated at reflux for 3 days. After being cooled to 0°C, the mixture was quenched with 1M aqueous HCl (15 mL) and extracted with Et_2O (3 x 200 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a

mixture of ethyl ester **430** and recovered sultam **436**. The crude residue was purified by SiO_2 flash chromatography (20:1 petrol:EtOAc) to afford ethyl ester **430** as a colorless oil (455 mg, 100%) and (5:1 petrol:EtOAc) to recover the auxiliary **373** (370 mg, 96%).[112]

$[\alpha]_D$ - 2.18° (*c* 1.01, CH_2Cl_2).

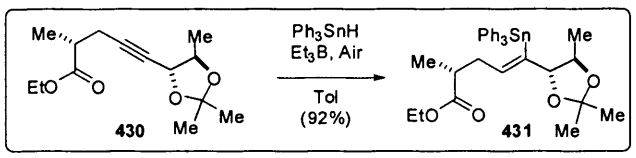
IR (neat film) 2984 (s), 2933 (m), 1736 (s), 1456 (w), 1431 (m), 1377 (m), 1234 (m), 1175 (s), 1099 (m), 1028 (s), 858 (w).

^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 4.08 (q, *J* = 7.1 Hz, 2 H, C<u>H</u>$_2$-O), 4.07 (dt, *J* = 8.1, 1.9 Hz, 1 H, C≡C-C<u>H</u>-O), 3.97 (qd, *J* = 8.1, 6.1 Hz, 1 H, CH_3-C<u>H</u>-O), 2.58 (m, 1 H, C<u>H</u>-CH_3), 2.45 (ddd, *J* = 16.7, 5.9, 1.9 Hz, 1 H, C<u>H</u>$_2$-CH), 2.36 (ddd, *J* = 16.7, 7.6, 1.9 Hz, 1H, C<u>H</u>$_2$-CH), 1.39 (s, 3 H, CC<u>H</u>$_3$), 1.36 (s, 3 H, C C<u>H</u>$_3$), 1.27 (d, *J* = 6.0 Hz, 3 H, C<u>H</u>$_3$-CH-O), 1.22 (t, *J* = 7.1 Hz, 3 H, C<u>H</u>$_3$CH$_2$O), 1.21 (d, *J* = 7.0 Hz, 3 H, C<u>H</u>$_3$CH).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 174.7 (C=O), 109.2 (<u>C</u>(CH$_3$)$_2$), 84.5 (<u>C</u>≡<u>C</u>), 77.6 (CH_3-<u>C</u>H-O), 72.1 (C≡C-<u>C</u>H-O), 60.5 (<u>C</u>H$_2$-O), 38.7 (<u>C</u>H-CH_3), 27.1 (C<u>C</u>H$_3$), 26.3 (C<u>C</u>H$_3$), 22.9 (<u>C</u>H$_2$-CH), 16.8 (<u>C</u>H$_3$CH), 16.3 (<u>C</u>H$_3$-CH-O), 14.2 (C<u>H</u>$_3$CH$_2$O).

FAB (+) HRMS: Calcd. for $C_{14}H_{22}NaO_4$: $(M+Na)^+$: *m/e* 277.14157; Found: *m/e* 277.14189.

Stannane 431



Ph_3SnH (1.77 g, 5.03 mmol) was weighed in a glove bag and added to a round-bottomed flask containing alkyne **430** (0.640 g, 2.52 mmol). The flask was immediately purged with N_2 and dry PhMe (2.52 mL) was added. Et_3B (1 M solutions in hexanes, 0.76 mL, 0.756 mmol) was then added dropwise. Air was injected into the reaction vessel to initiate the reaction. The reactants were stirred at rt overnight. H_2O (30 mL) was added and the mixture

was extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by SiO_2 flash chromatography (gradient elution: 100:1 to 25:1 petrol:EtOAc) to afford the vinylstannane **431** as a single isomer in the form of a colorless oil (1.40 g, 92%).[105]

$[\alpha]_D$ - 19.1° (*c* 0.42, CH_2Cl_2).

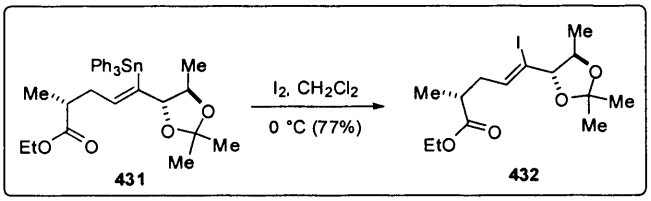
IR (neat film) 3059 (w), 2980 (s), 2931 (m), 2866 (w), 1732 (s), 1454 (w), 1431 (m), 1375 (s), 1229 (m), 1180 (s), 1095 (m), 1026 (m), 858 (w), 731 (s), 700 (s).

^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 7.56 (m, 6 H, Ar), 7.32 (m, 9 H, Ar), 6.55 (ddd, *J* = 8.4, 6.4, 1.2 Hz (^3J ^{117}Sn-^{1}H = 150 Hz), 1 H, H$\underline{C}$=CSn), 3.16 (dd, *J* = 8.4, 1.1 Hz, 1 H, SnC-C$\underline{H}$-O), 4.01 (q, *J* = 7.2, 1.7 Hz, 2 H, C$\underline{H_2}$-O), 3.73 (qd, *J* = 8.4, 1.7 Hz, 1 H, CH_3-C$\underline{H}$-O), 2.32 (m, 1 H, C$\underline{H_2}$-CH), 2.13 (m, 2 H, C$\underline{H_2}$-CH, C$\underline{H}$-CH_3), 1.25 (s, 3 H, CC$\underline{H_3}$), 1.19 (d, *J* = 6.0 Hz, 3 H, C$\underline{H_3}$-CH-O), 1.16 (t, *J* = 7.1 Hz, 3 H, C$\underline{H_3}$$CH_2O$), 0.72 (d, *J* = 6.9 Hz, 3 H, C$\underline{H_3}$CH), 0.66 (s, 3 H, CC$\underline{H_3}$).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 175.4 (C=O), 144.7 (H$\underline{C}$=CSn), 139.6 (HC=$\underline{C}$Sn), 137.0 (Ar), 128.9 (Ar), 128.7 (Ar), 108.0 ($\underline{C}(CH_3)_2$), 89.3 (SnC-$\underline{C}$H-O), 77.1 (CH_3-$\underline{C}$H-O), 60.2 ($\underline{C}H_2O$), 39.8 ($\underline{C}$H-CH_3), 37.4 ($\underline{C}H_2$CH=), 27.2 (C$\underline{C}H_3$), 25.9 (C$\underline{C}H_3$), 16.6 ($\underline{C}H_3$CH), 16.5 ($\underline{C}H_3$CHO), 14.2 ($\underline{C}H_3CH_2O$).

FAB (+) HRMS: Calcd. for $C_{32}H_{38}NaO_4Sn$: $(M+Na)^+$: *m/e* 629.16896; Found: *m/e* 629.16654.

Iodide 432



To a stirred solution of vinyl triphenylstannane **431** (1.2 g, 2.00 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C under N_2 was added solid I_2 (0.604 g, 2.38 mmol) in one portion. The mixture was stirred at rt for 1 h. The solvent was removed *in vacuo* and the residue purified by SiO_2 flash

chromatography (gradient elution: 40:1 to 10:1 petrol:EtOAc) to give vinyl iodide **432** as a pale yellow oil (0.600 g, 77 %).[107]

$[\alpha]_D$ + 4.8° (*c* 1.19, CH_2Cl_2).

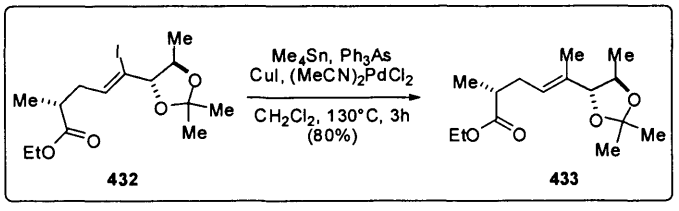
IR (neat film) 3439 (w), 2995 (s), 2931 (m), 2908 (s), 1732 (s), 1454 (w), 1377 (m), 1234 (m), 1178 (s), 1101 (m), 1036 (m), 860 (w).

^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 6.07 (ddd, *J* = 7.2, 6.3, 0.9 Hz, 1 H, H$\underline{C}$=Cl), 4.10 (q, *J* = 7.2 Hz, 2 H, C$\underline{H_2}$-O), 3.97 (qd, *J* = 8.0, 6.0 Hz, 1 H, CH_3-C$\underline{H}$-O), 3.55 (d, *J* = 8.0 Hz, 1 H, IC-C$\underline{H}$-O), 2.56 (m, 1 H, C$\underline{H}$-CH_3), 2.52 (m, 1 H, C$\underline{H_2}$-CH), 2.39 (m, C$\underline{H_2}$-CH), 1.48 (s, 3 H, CC$\underline{H_3}$), 1.40 (s, 3 H, CC$\underline{H_3}$), 1.26 (d, *J* = 6.0 Hz, 3 H, C$\underline{H_3}$CHO), 1.22 (t, *J* = 7.1 Hz, 3 H, C$\underline{H_3}$$CH_2O$), 1.17 (d, *J* = 6.9 Hz, 3 H, C$\underline{H_3}$CH).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 175.4 (C=O), 136.6 (H$\underline{C}$=Cl), 109.1 ($\underline{C}(CH_3)_2$), 108.6 (HC=$\underline{C}$l), 87.7 (C=IC-$\underline{C}$H-O), 76.8 (CH_3-$\underline{C}$H-O), 60.5 ($\underline{C}H_2$-O), 39.3 ($\underline{C}H_2$CH=), 38.5 ($\underline{C}$H-CH_3), 27.7 (C$\underline{C}H_3$), 27.0 (C$\underline{C}H_3$), 16.9 ($\underline{C}H_3$CH), 16.7 ($\underline{C}H_3$-CH-O), 14.2 ($\underline{C}H_3CH_2O$).

FAB (+) HRMS: Calcd. for $C_{14}H_{23}INaO_4$: $(M+Na)^+$: *m/e* 405.05387; Found: *m/e* 405.054665.

Alkene 433



432 **433**

To a solution of vinyl iodide **432** (600 mg, 1.53 mmol) in dry DMF (15.3 mL) and freshly distilled Et_3N (15.3 mL, 109 mmol) at rt under N_2 was added Me_4Sn (0.70 mL, 5.05 mmol), CuI (29 mg, 0.153 mmol), and Ph_3As (47 mg, 0.153 mmol) followed by $(CH_3CN)_2PdCl_2$ (39 mg, 0.153 mmol). The reactants were heated at 130 °C for 3 h, cooled to rt, and H_2O (50 mL) was added. After extraction with Et_2O (3 x 100 mL), the combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by SiO_2 flash

chromatography (gradient elution: 100:1 to 20:1 petrol:EtOAc) to afford alkene **433** in the form of a colorless oil (330 mg, 80%).[107]

$[\alpha]_D$ - 8.1° (*c* 0.26, CH_2Cl_2).

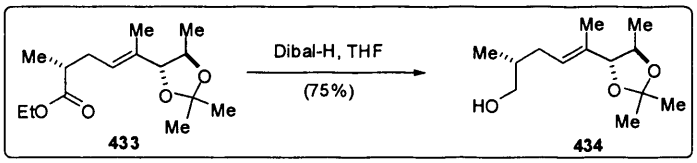
IR (neat film) 2980 (s), 2931 (m), 2878 (w), 1734 (s), 1456 (w), 1375 (m), 1240 (m), 1173 (m), 1097 (m), 1034 (m), 864 (w).

^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 5.45 (t, *J* = 6.9 Hz, 1 H, HC=CMe), 4.09 (q, *J* = 7.2 Hz, 2 H, CH_2-O), 3.82 (m, 1 H, CH_3-CH-O), 3.80 (m, 1 H, C=C-CH-O), 2.45 (m, 1 H, CH-CH_3), 2.38 (m, 1 H, CH_2-CH), 2.20 (m, 1 H, CH_2-CH), 1.63 (s, 1 H, C=CCH_3), 1.39 (s, 6 H, C(CH_3)$_2$), 1.22 (t, *J* = 7.1Hz, 3 H, CH_3CH_2O), 1.18 (d, *J* = 5.6 Hz, 3 H, CH_3CHO), 1.11 (d, *J* = 7.0 Hz, 3 H, CH_3CH).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 176.0 (C=O), 133.1 (MeC=CH), 126.4 (HC=CMe), 108.0 (C(CH_3)$_2$), 88.3 (C=C-CH-O), 74.5 (CH_3-CH-O), 60.3 (CH_2-O), 39.4 (CH-CH_3), 31.7 (CH_2CH=), 27.5 (CCH_3), 26.8 (CCH_3), 17.0 (CH_3CH), 16.4 (CH_3CHO), 14.2 (CH_3CH_2O), 11.8 (C=CCH_3).

FAB (+) HRMS: Calcd. for $C_{15}H_{26}NaO_4$: $(M+Na)^+$: *m/e* 293.17287; Found: *m/e* 293.17287.

Alcohol 434



To a solution of alkene **433** (190 mg, 0.703 mmol) in dry THF (2.34 mL) at rt under N_2 was added dropwise over 5 min a solution of DIBAL-H (1.5 M in toluene, 1.16 mL, 1.75 mmol). The reaction mixture was stirred for 1 h and a saturated aqueous solution of Rochelle's salt (10 mL) and ether (10 mL) were added. The resulting mixture was stirred at rt for 1 h and extracted with Et_2O (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by SiO_2 flash chromatography (gradient elution: 10:1 to 6:1 petrol:EtOAc) to afford alcohol **434** as a white foam (1.20 g, 75%).

$[\alpha]_D$ + 7.4° (*c* 0.68, CH_2Cl_2).

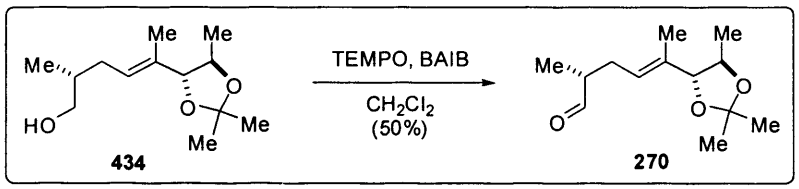
IR (neat film) 3433 (br), 2980 (s), 2928 (m), 2878 (m), 1726 (w), 1454 (w), 1377 (m), 1238 (s), 1175 (m), 1095 (m), 1034 (s), 862 (w).

^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 5.50 (qd, *J* = 6.9 Hz, 1 H, HC=CMe), 3.84 (m, 1 H, CH_3-CH-O), 3.82 (m, 1 H, =C-CH-O), 3.47 (dd, *J* = 6.1, 10.6 Hz, 1 H, CH_2OH), 3.41 (dd, *J* = 6.1, 10.6 Hz, 1 H, CH_2OH), 2.16 (m, 1 H, CH_2-CH), 1.89 (m, 1 H, CH_2-CH), 1.68 (m, 1 H, CH-CH_3), 1.62 (s, 1 H, C=CCH_3), 1.39 (s, 6 H, C(CH_3)$_2$), 1.18 (d, *J* = 5.6 Hz, 3 H, CH_3CHO), 0.88 (d, *J* = 6.8 Hz, 3 H, CH_3CH).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 132.0 (HC=CMe), 128.3 (HC=CMe), 107.9 (C(CH_3)$_2$), 88.7 (C=C-CH-O), 74.3 (CH_3-CH-O), 67.7 (CH_2-O), 36.1 (CH-CH_3), 31.4 (CH_2CH=), 27.4 (CCH_3), 26.7 (CCH_3), 17.0 (CH_3CH), 16.4 (CH_3CHO), 11.5 (C=CCH_3).

FAB (+) HRMS: Calcd. for $C_{13}H_{24}NaO_3$: $(M+Na)^+$: *m/e* 251.16231; Found: *m/e* 251.16182.

Aldehyde 210



To a solution of alcohol **434** (0.10 g, 0.271 mmol) in dry CH_2Cl_2 (2.7 mL) under N_2 was added TEMPO radical (6.8 mg, 0.044 mmol) followed by [bis(acetoxy)iodo]benzene (141 mg, 0.439 mmol) in one portion. The reaction mixture was stirred at rt for 5 h, quenched with sat. aq. $Na_2S_2O_3$ (5 mL) and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by SiO_2 flash chromatography (gradient elution: 5:1 to 1:1 petrol:EtOAc) to afford aldehyde **270** as a colorless oil (50 mg, 50%).[104]

^{1}H-NMR (500 MHz, $CDCl_3$, 298K) δ 9.64 (d, *J* = 1.3 Hz, 1 H, C<u>H</u>O), 5.47 (dddd, *J* = 6.9 Hz, 1 H, <u>H</u>C=CMe), 3.83 (m, 1 H, CH_3-C<u>H</u>-O), 3.82 (m, 1 H, C=C-C<u>H</u>-O), 2.43 (m, 2 H, C<u>H_2</u>-CH), 2.17 (m, 1 H, C<u>H</u>-CH_3), 1.65 (s, 1 H, C=CC<u>H_3</u>), 1.40 (s, 6 H, C(C<u>H_3</u>)$_2$), 1.19 (d, *J* = 5.6 Hz, 3 H, C<u>H_3</u>CHO), 1.08 (d, *J* = 7.0 Hz, 3 H, C<u>H_3</u>CH).

^{13}C-NMR (125 MHz, $CDCl_3$, 298K) δ 204.3 (<u>C</u>HO), 133.6 (Me<u>C</u>=CH), 125.8 (H<u>C</u>=CMe), 108.0 (<u>C</u>(CH_3)$_2$), 88.7 (C=C-<u>C</u>H-O), 74.3 (CH_3-<u>C</u>H-O), 46.3 (<u>C</u>H-CH_3), 31.4 (<u>C</u>H_2CH=C), 27.4 (C<u>C</u>H_3), 26.8 (C<u>C</u>H_3), 17.0 (<u>C</u>H_3CHO), 13.0 (<u>C</u>H_3CH), 11.7 (C=C<u>C</u>H_3).

FAB (+) HRMS: Calcd. for $C_{13}H_{22}NaO_3$: $(M+Na)^+$: *m/e* 249.14666 ; Found: *m/e* 249.14601.

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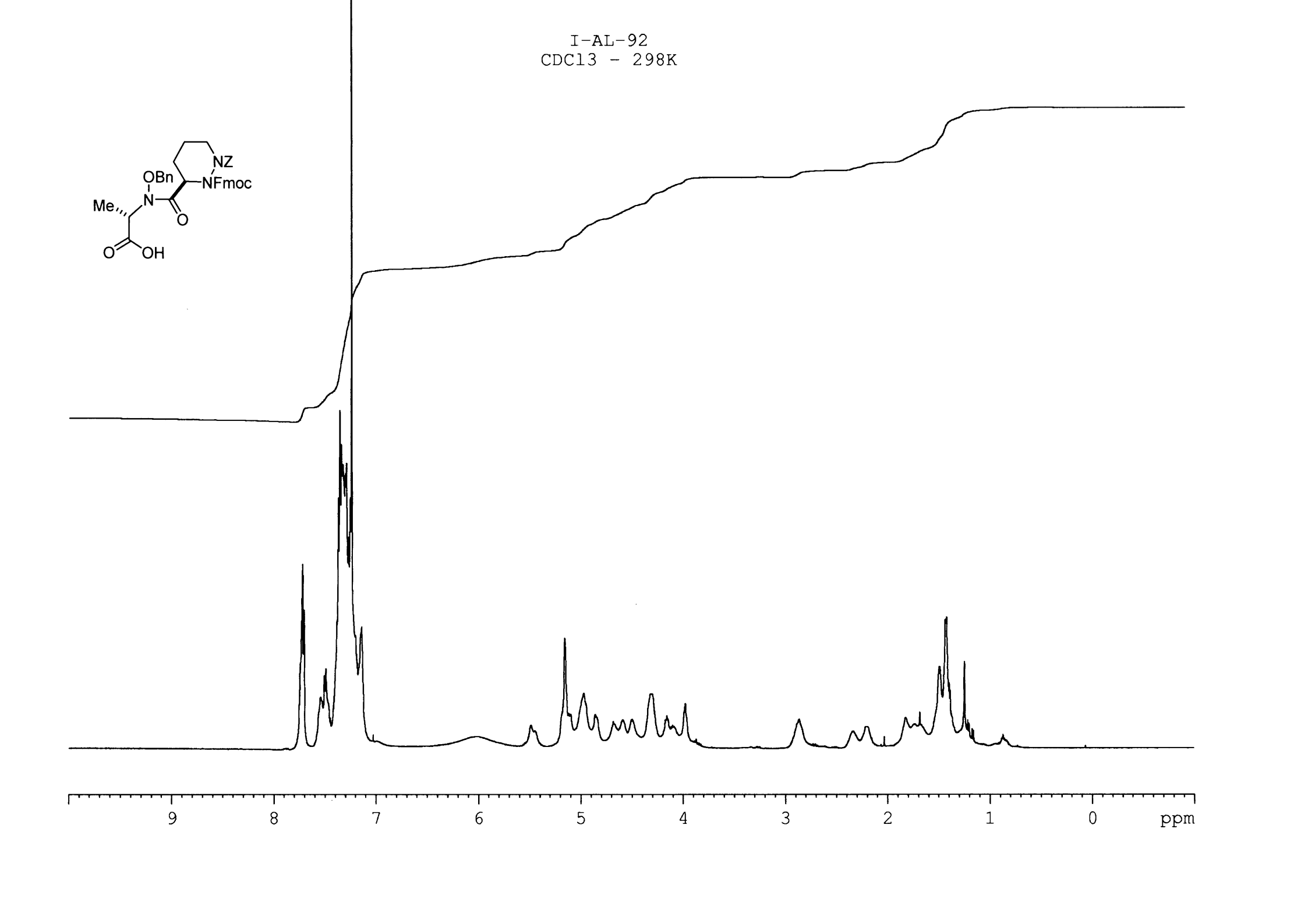
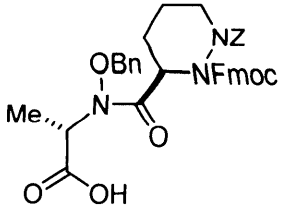
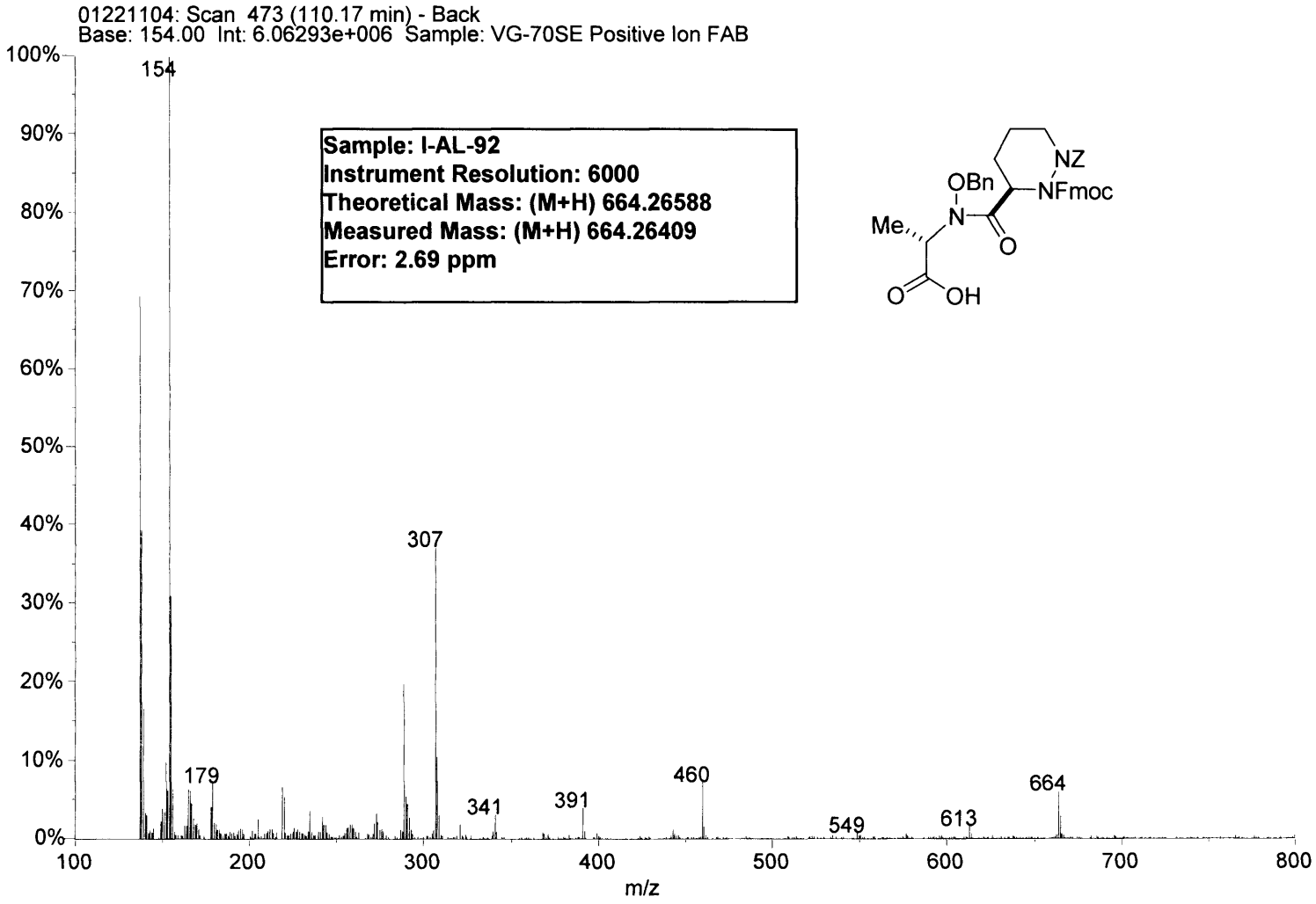
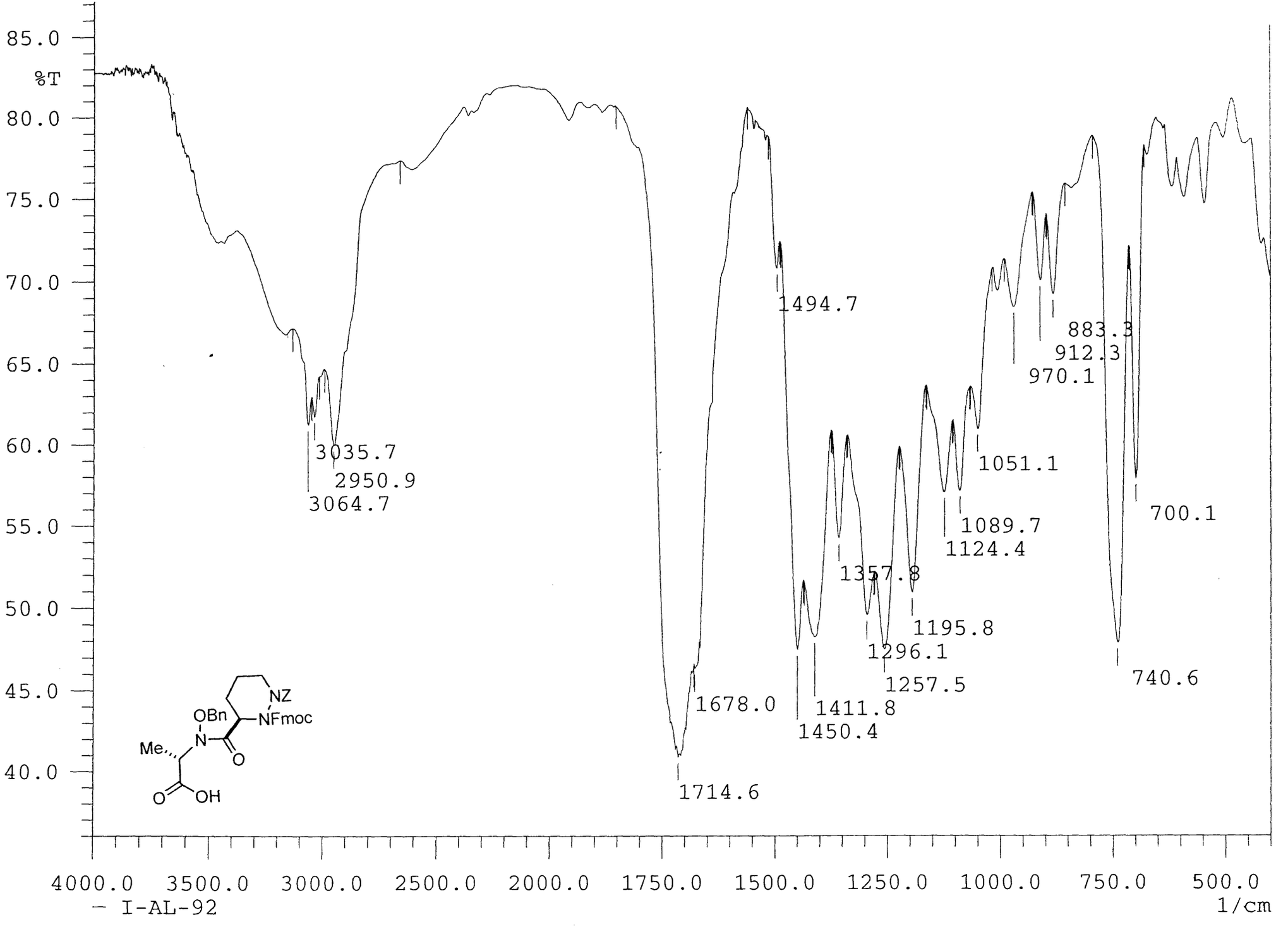
APPENDIX

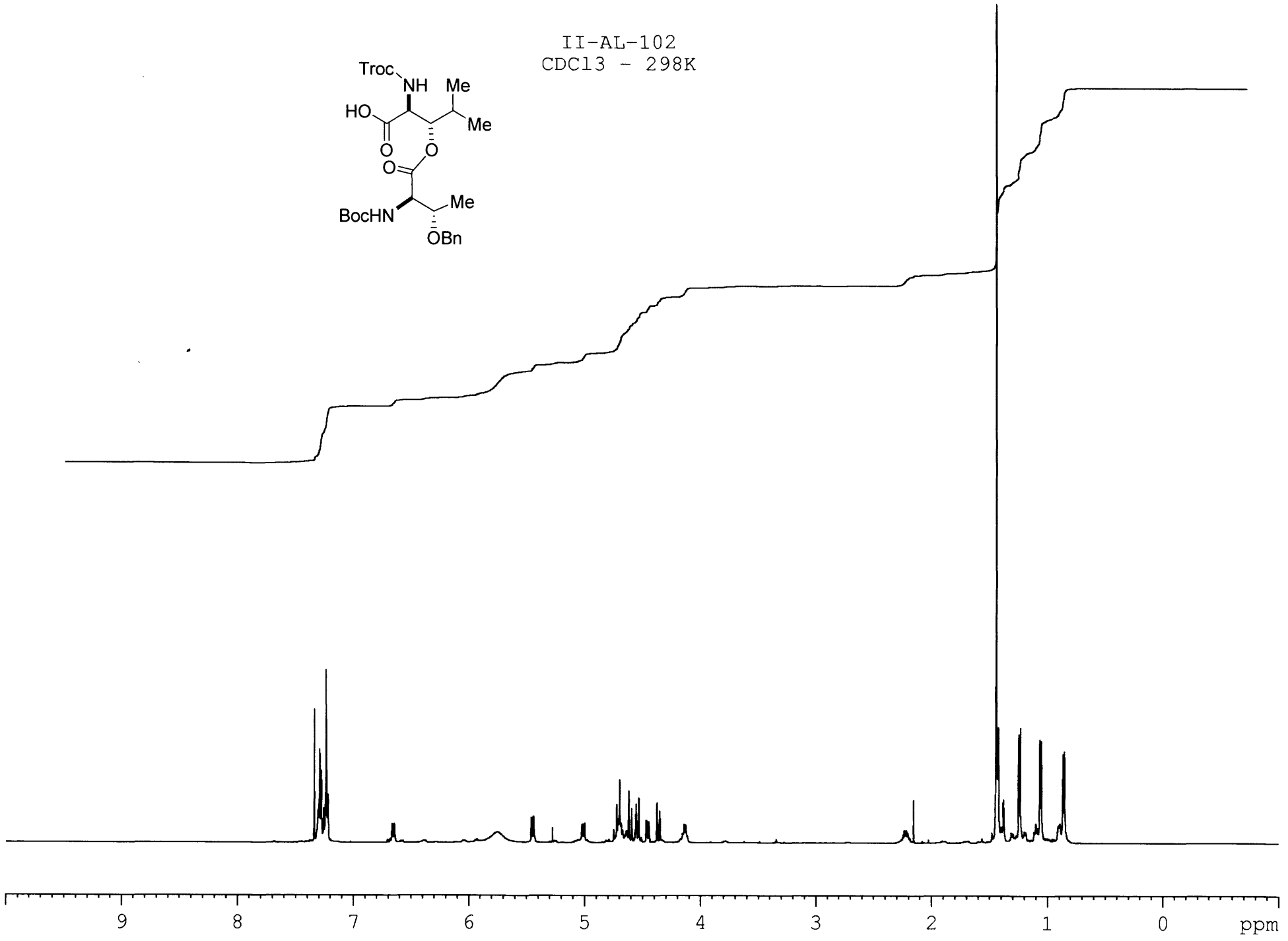

I-AL-92
CDCl3 - 298K
NZ
OBn
NFmoc
Me
N
O
O
OH
9
8
7
6
5
4
3
2
1
0
ppm

I-AL-92
13C
CDCl3 - 298K

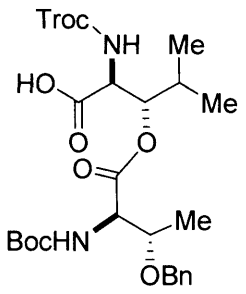


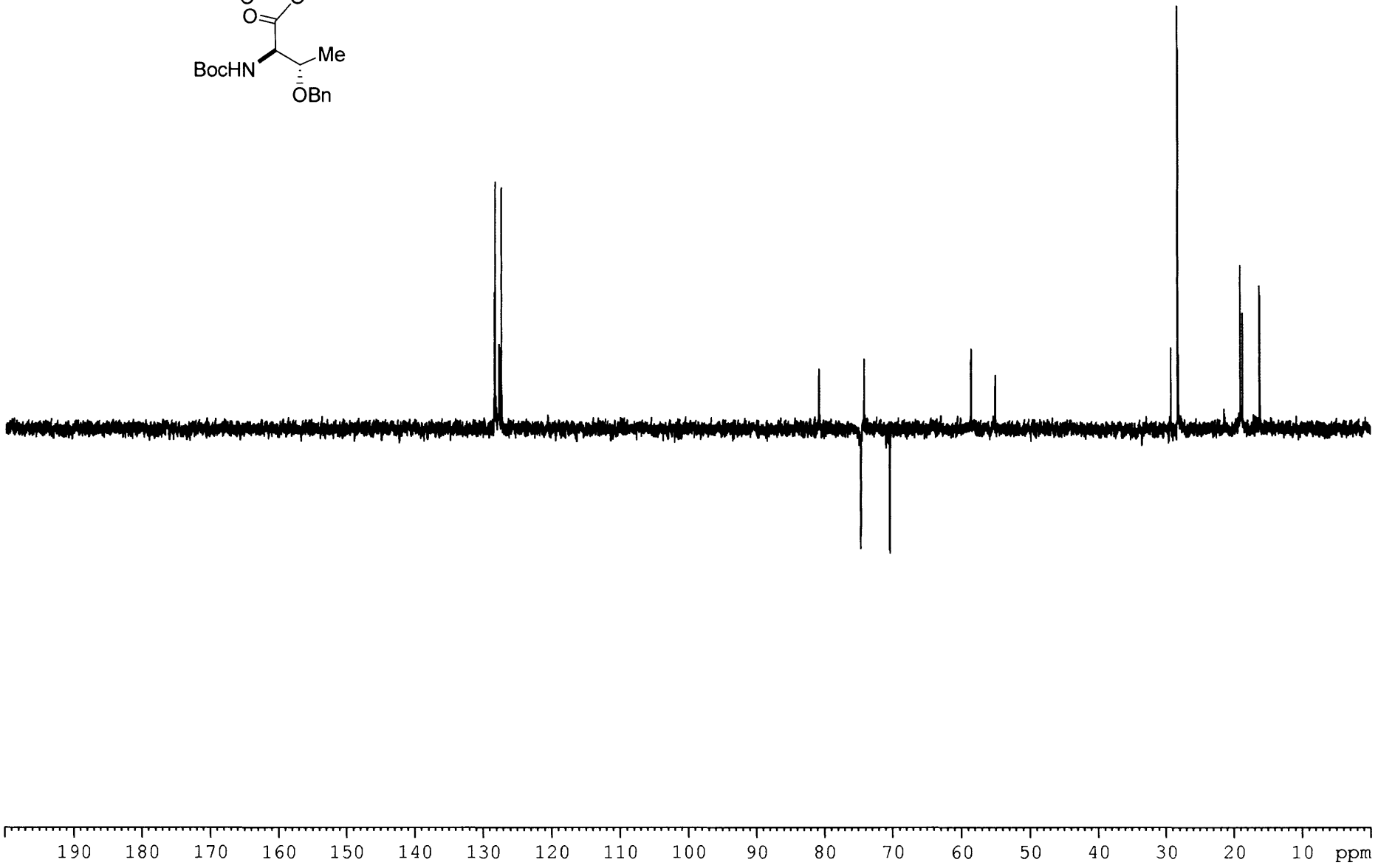

01221104: Scan 473 (110.17 min) - Back
Base: 154.00 Int: 6.06293e+006 Sample: VG-70SE Positive Ion FAB
Sample: I-AL-92
Instrument Resolution: 6000
Theoretical Mass: (M+H) 664.26588
Measured Mass: (M+H) 664.26409
Error: 2.69 ppm
NZ
OBn
NFmoc
Me
N
O
O
OH
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
154
307
179
341
391
460
549
613
664
100
200
300
400
500
600
700
800
m/z


85.0
%T
80.0
75.0
70.0
65.0
60.0
55.0
50.0
45.0
40.0
3064.7
3035.7
2950.9
1714.6
1678.0
1494.7
1450.4
1411.8
1357.8
1296.1
1257.5
1195.8
1124.4
1089.7
1051.1
970.1
912.3
883.3
740.6
700.1
NZ
NFmoc
OBn
N
Me
O
O
OH
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
- I-AL-92

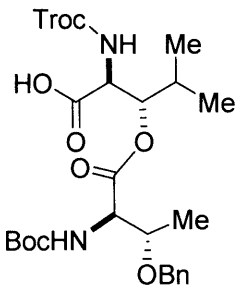

II-AL-102
CDCl3 - 298K
Troc
NH
Me
HO
Me
O
O
O
BocHN
Me
OBn
9
8
7
6
5
4
3
2
1
0
ppm

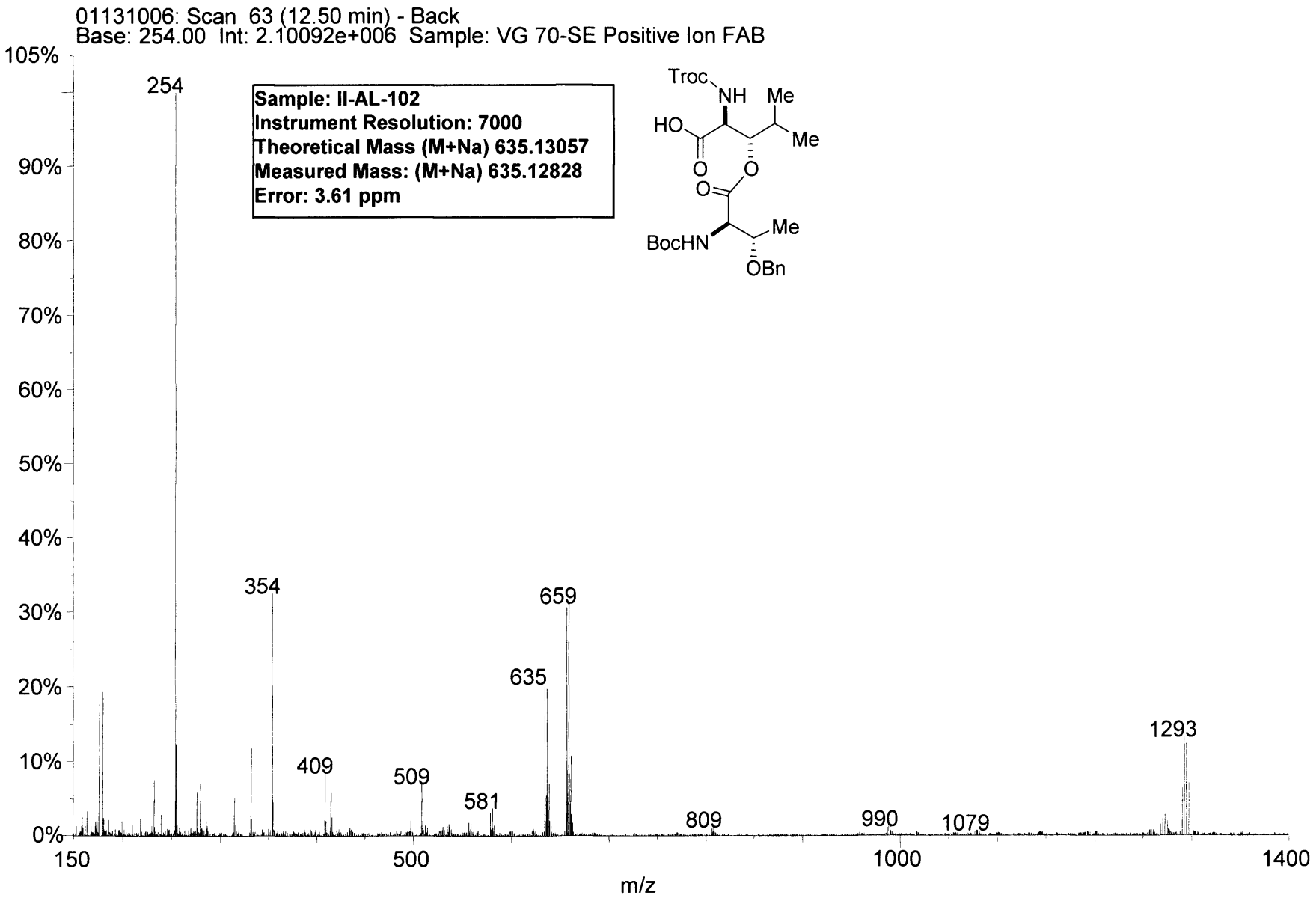
II-AL-102
DEPT
CDCl3 - 298K

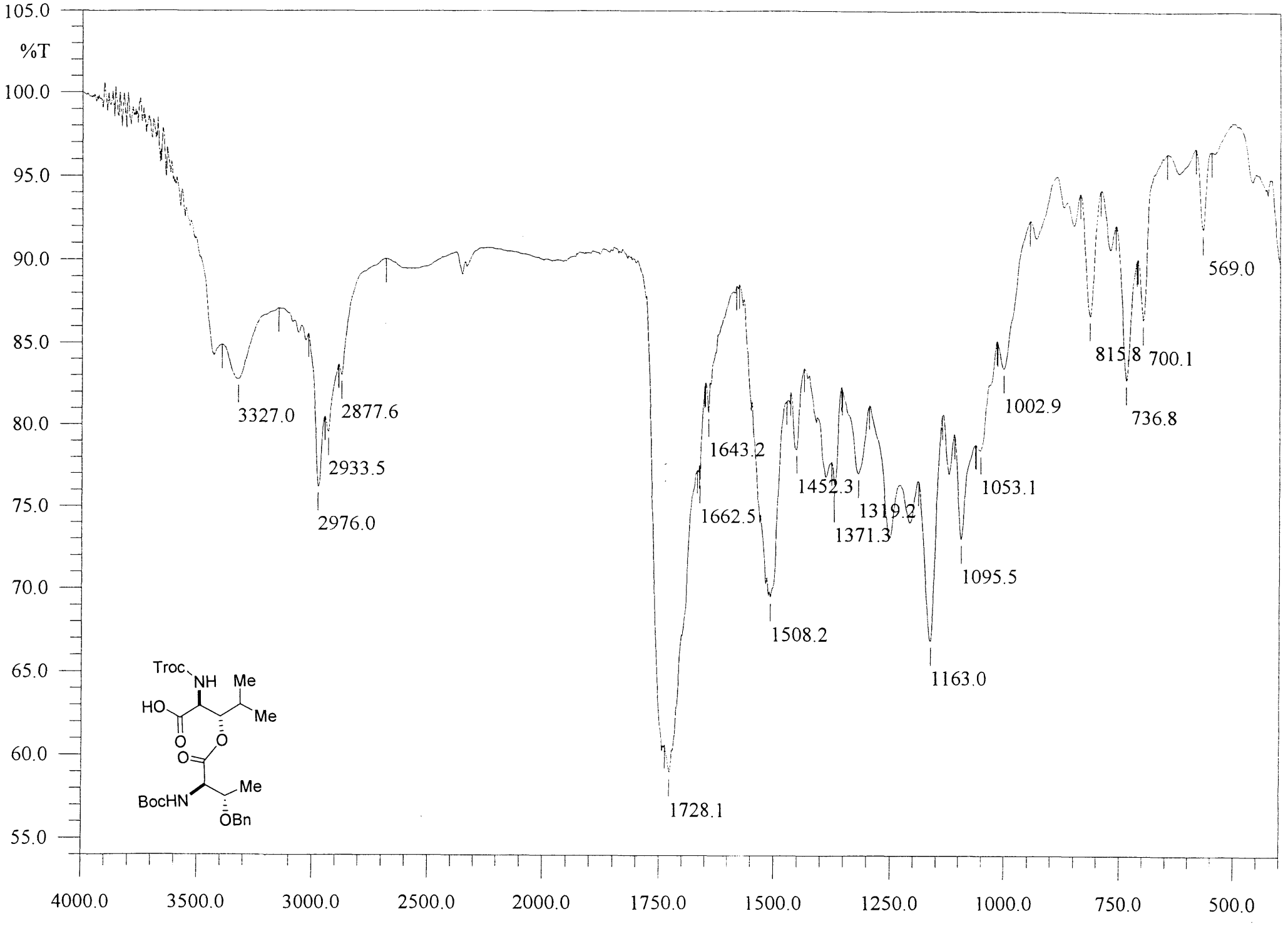




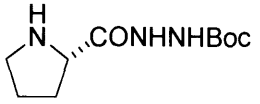
II-AL-102
13C
CDCl3 - 298K



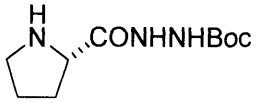

01131006: Scan 63 (12.50 min) - Back
Base: 254.00 Int: 2.10092e+006 Sample: VG 70-SE Positive Ion FAB
Sample: II-AL-102
Instrument Resolution: 7000
Theoretical Mass (M+Na) 635.13057
Measured Mass: (M+Na) 635.12828
Error: 3.61 ppm
Troc
NH
Me
HO
Me
O
O
O
Me
BocHN
OBn
105%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
254
354
409
509
581
635
659
809
990
1079
1293
150
500
1000
1400
m/z

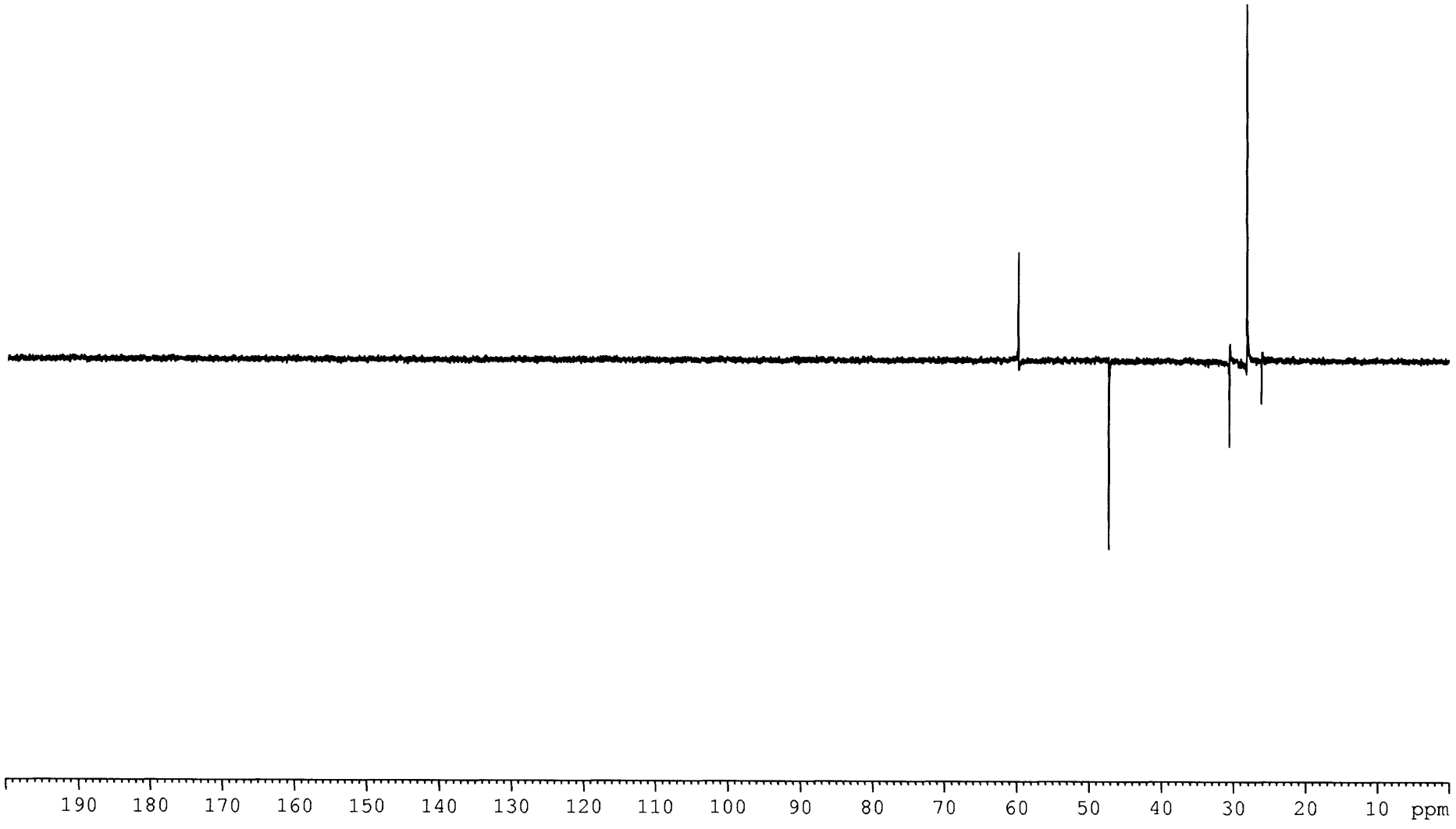

105.0
%T
100.0
95.0
90.0
85.0
80.0
75.0
70.0
65.0
60.0
55.0
3327.0
2877.6
2933.5
2976.0
1643.2
1662.5
1452.3
1319.2
1371.3
1508.2
1728.1
1163.0
1095.5
1053.1
1002.9
815.8
700.1
736.8
569.0
Troc
NH
Me
HO
Me
O
O
O
Me
BocHN
OBn
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0

I-AL-49
CDCl3 - 298K

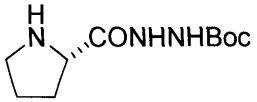


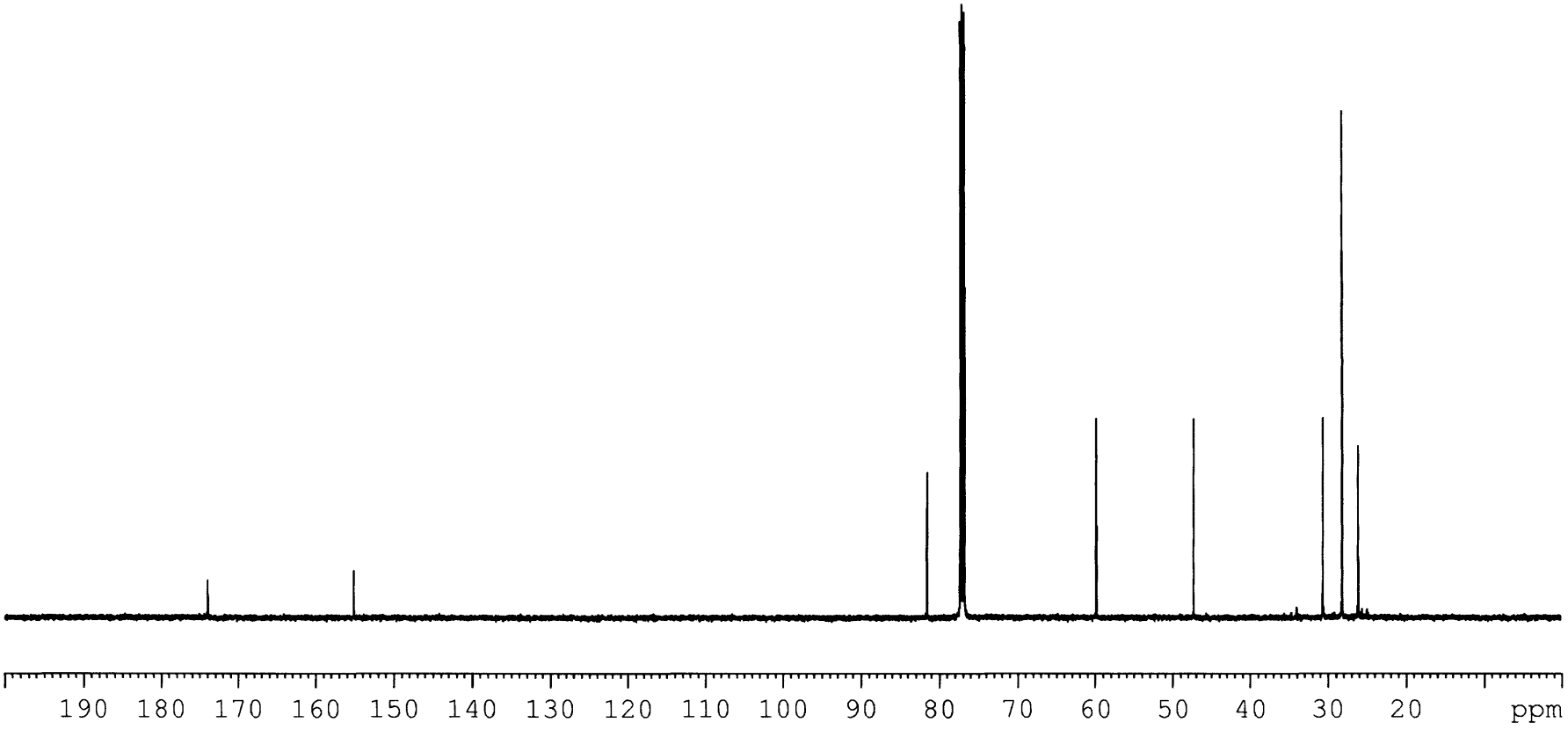
I-AL-49
CDCl3 - 298K
DEPT

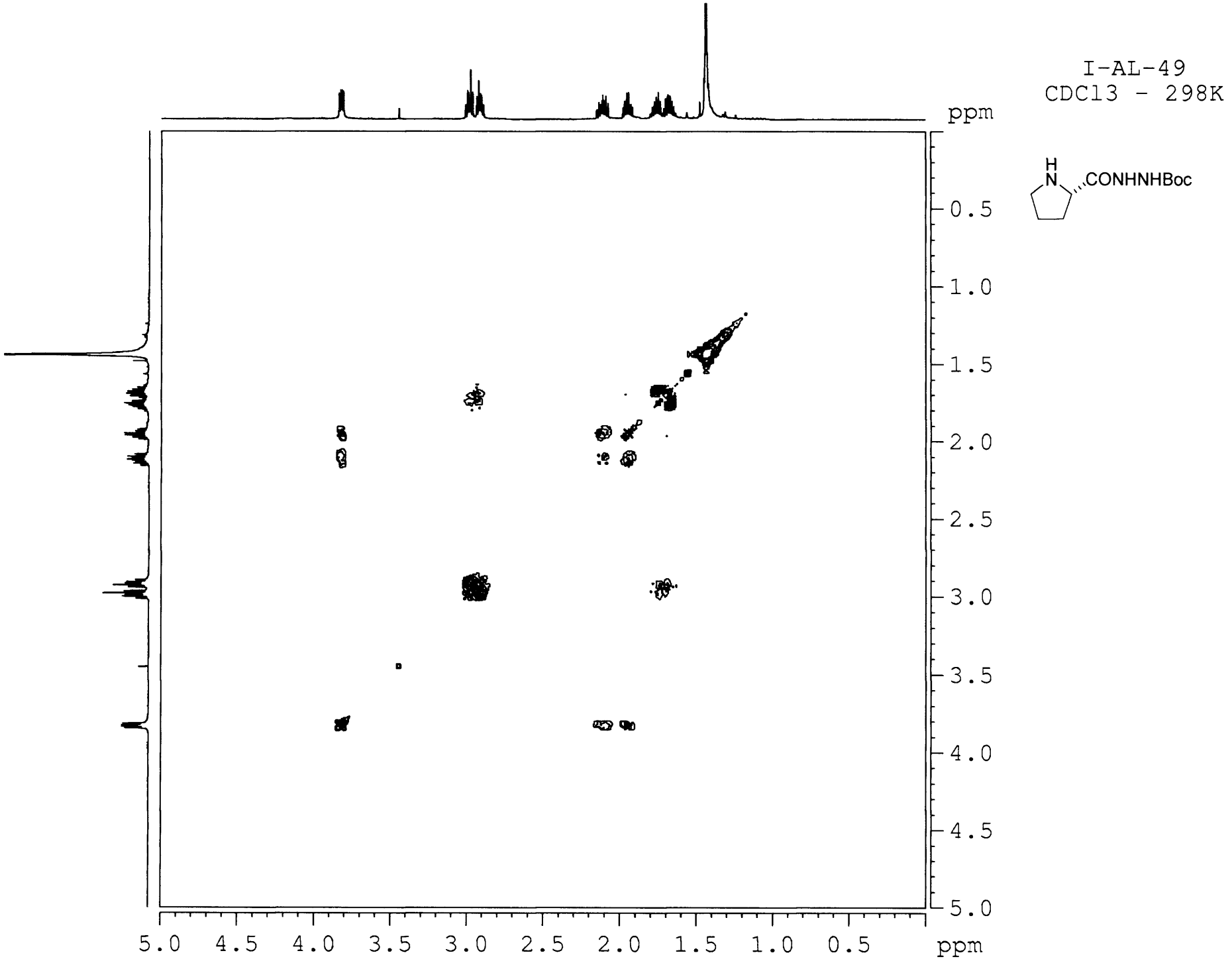


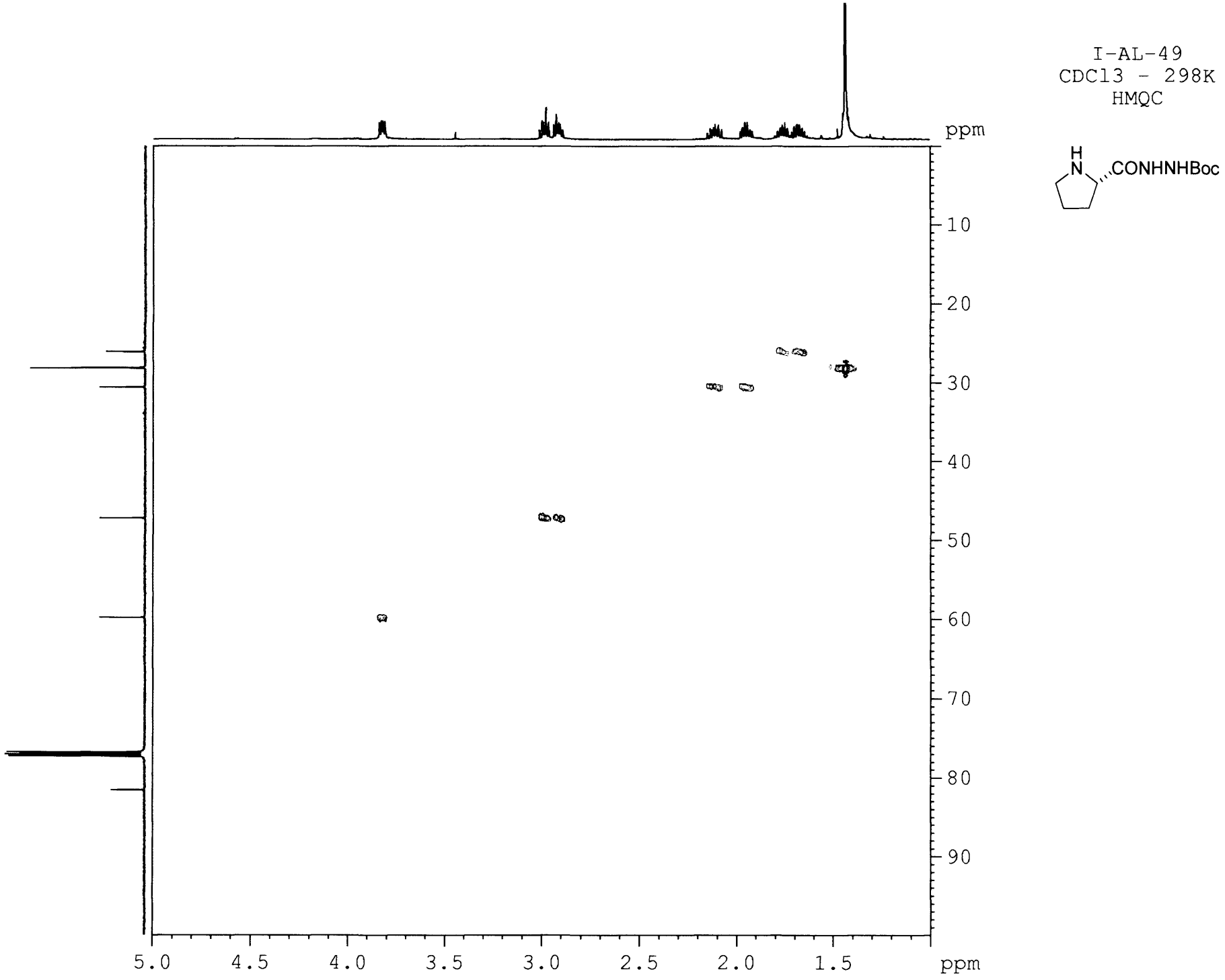


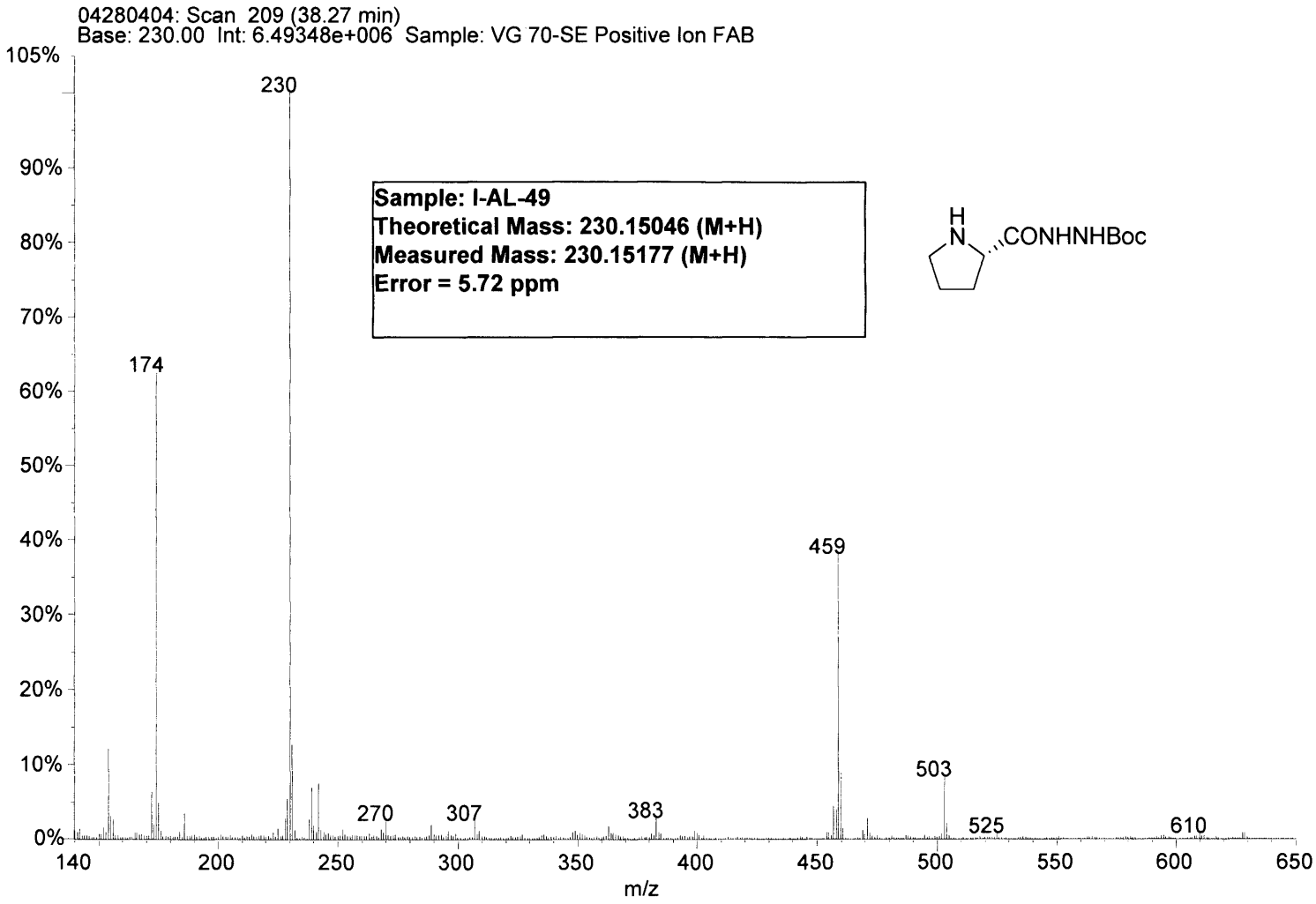
I-AL-49
CDCl3 - 298K
13C

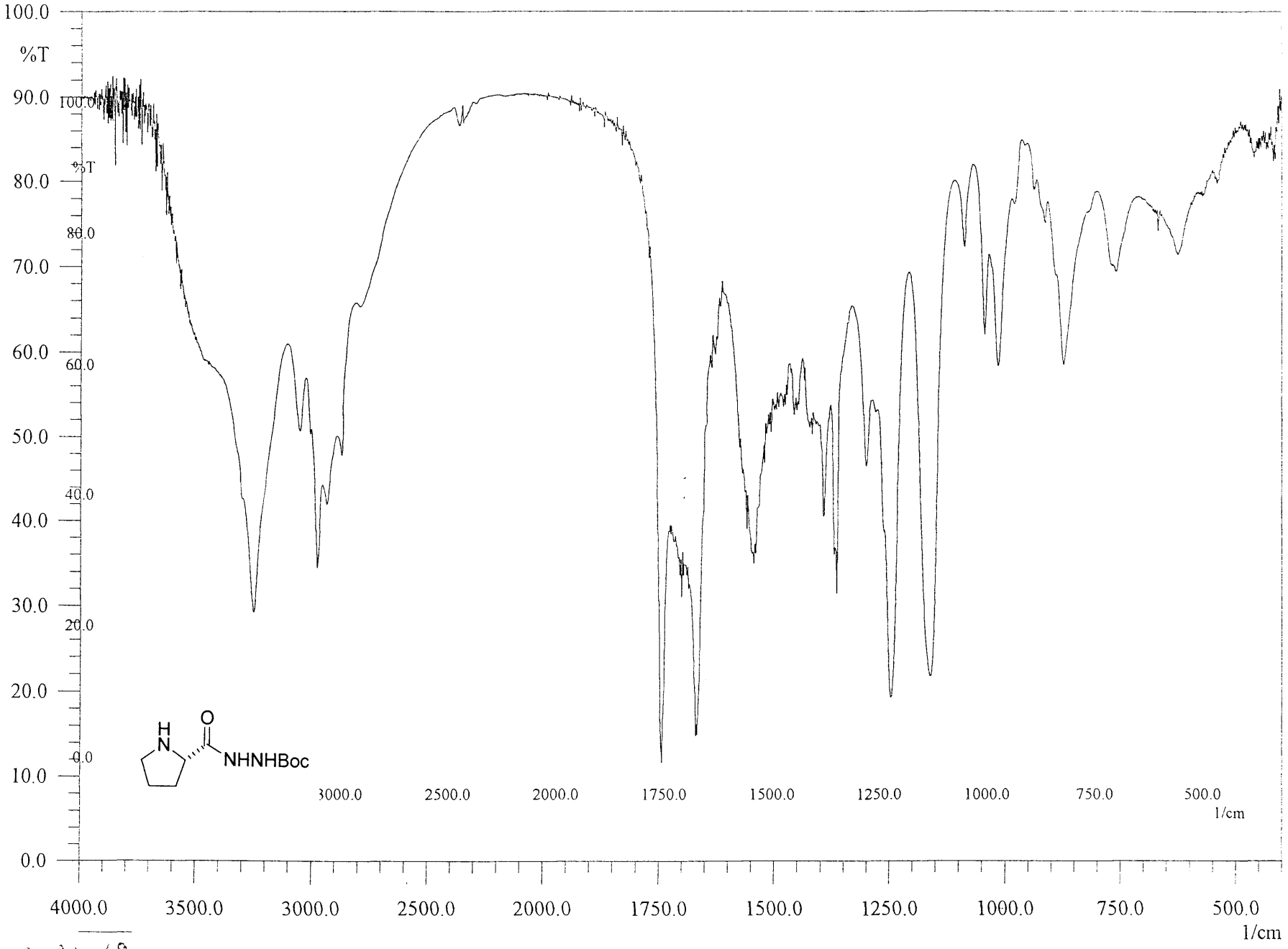




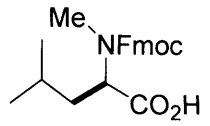

I-AL-49
CDCl3 - 298K
H
N
CONHNHBoc
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm


I-AL-49
CDCl3 - 298K
HMQC
H
N
CONHNHBoc
ppm
10
20
30
40
50
60
70
80
90
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

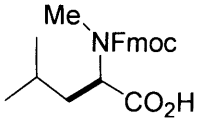

04280404: Scan 209 (38.27 min)
Base: 230.00 Int: 6.49348e+006 Sample: VG 70-SE Positive Ion FAB
105%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
230
174
459
503
270
307
383
525
610
140
200
250
300
350
400
450
500
550
600
650
m/z
Sample: I-AL-49
Theoretical Mass: 230.15046 (M+H)
Measured Mass: 230.15177 (M+H)
Error = 5.72 ppm
H
N
CONHNHBoc

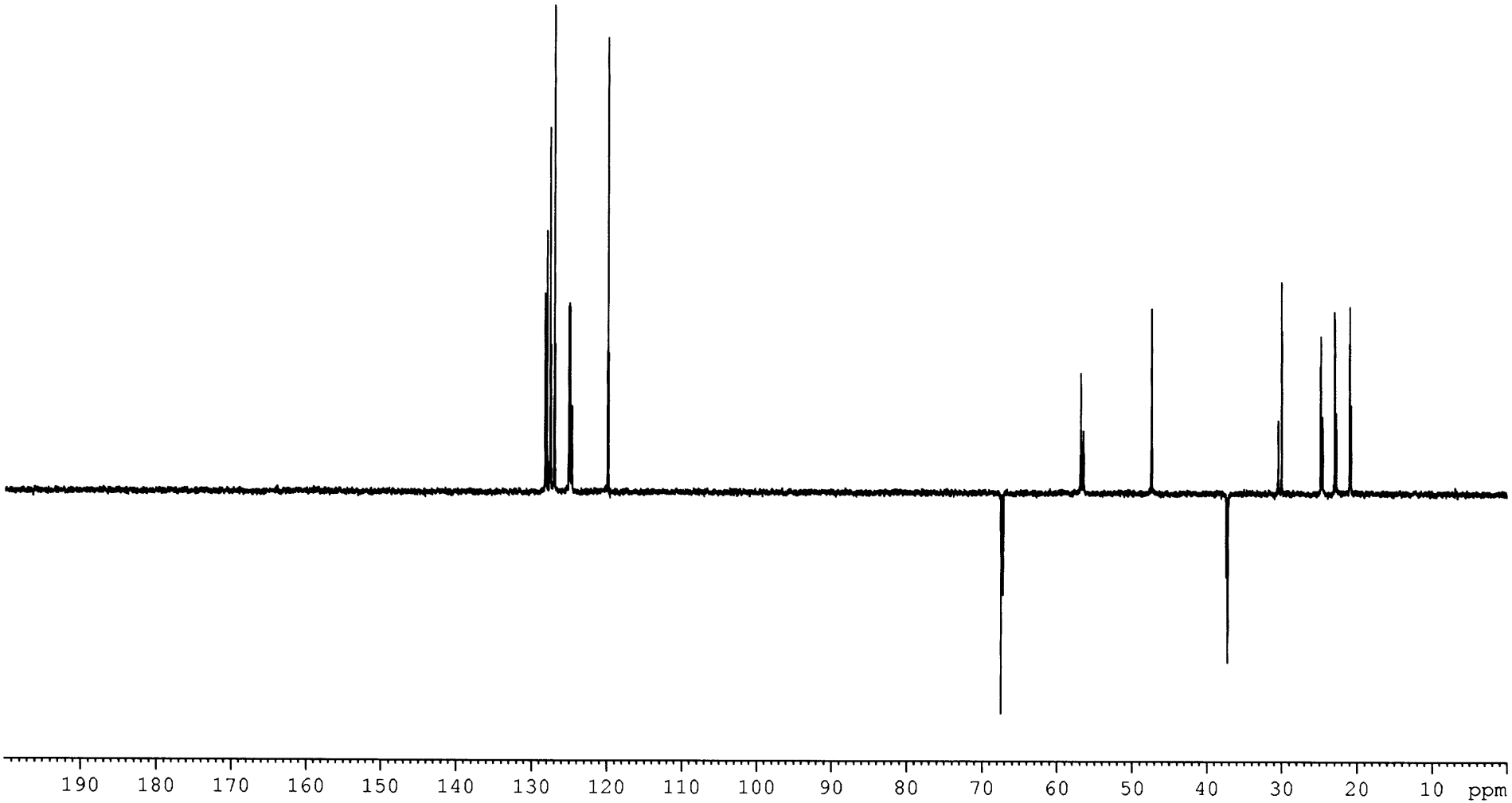

100.0
%T
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
H
N
O
NHNHBoc

I-AL-50
C6D6 - 298K

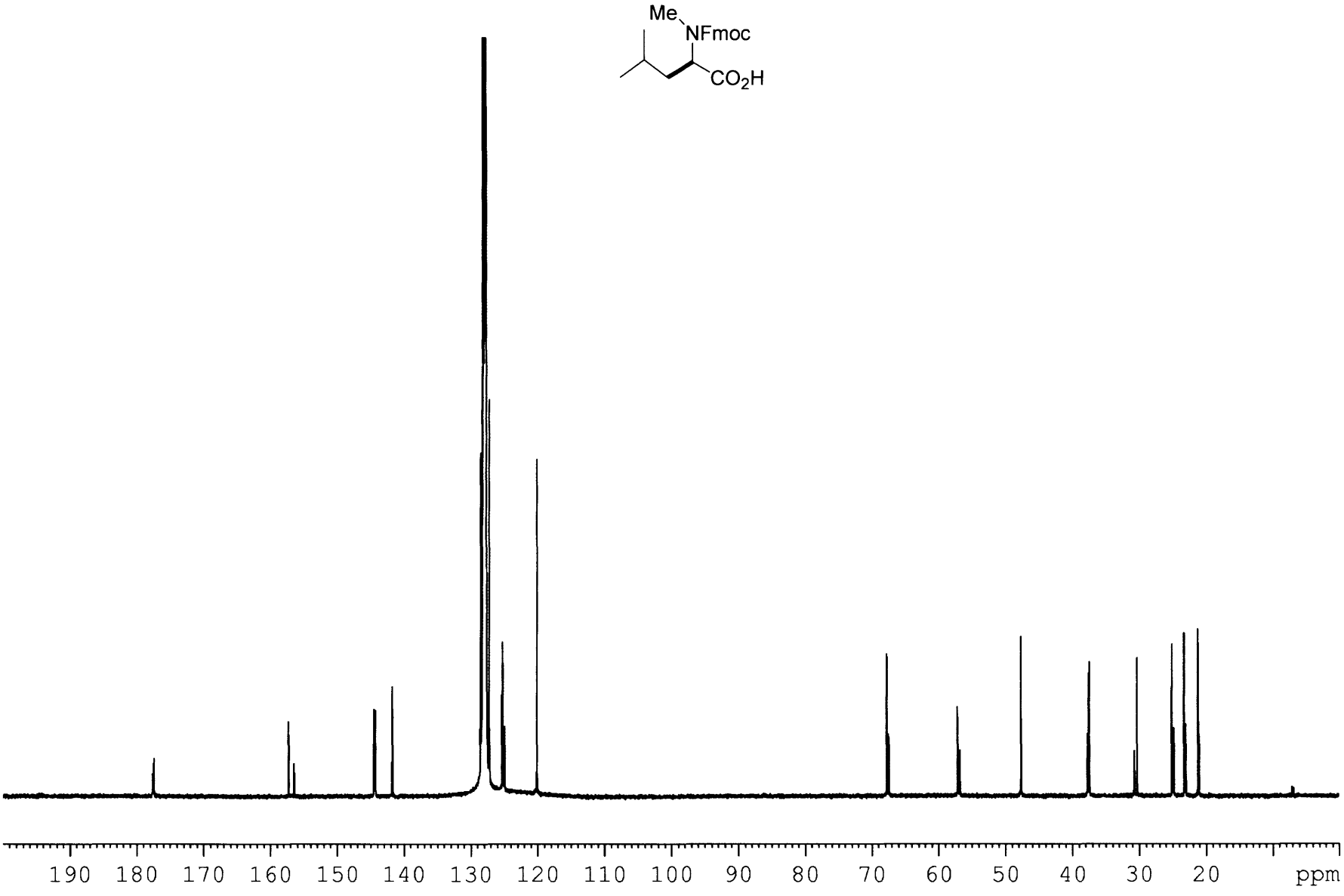


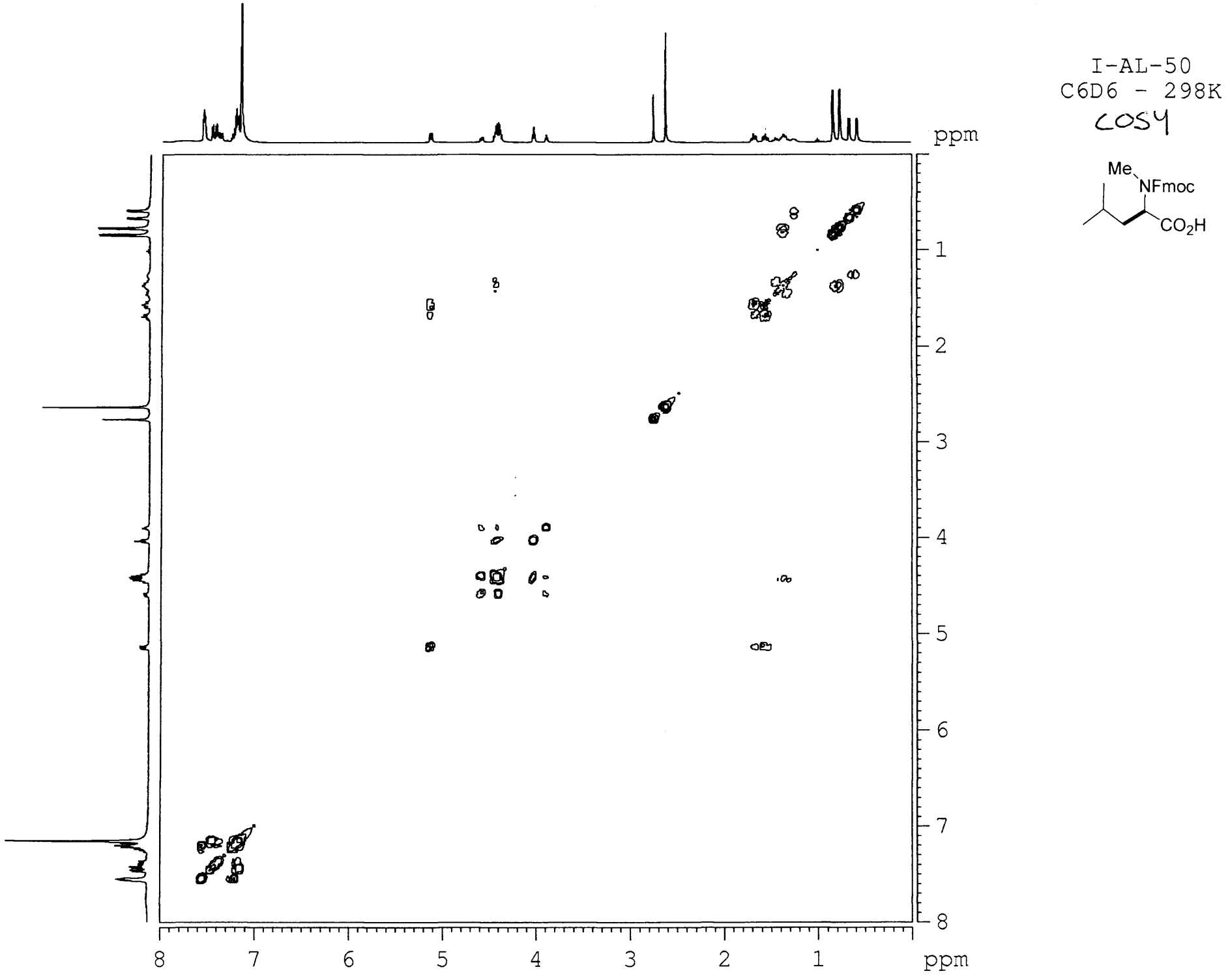
I-AL-50
C6D6 - 298K
CEPT



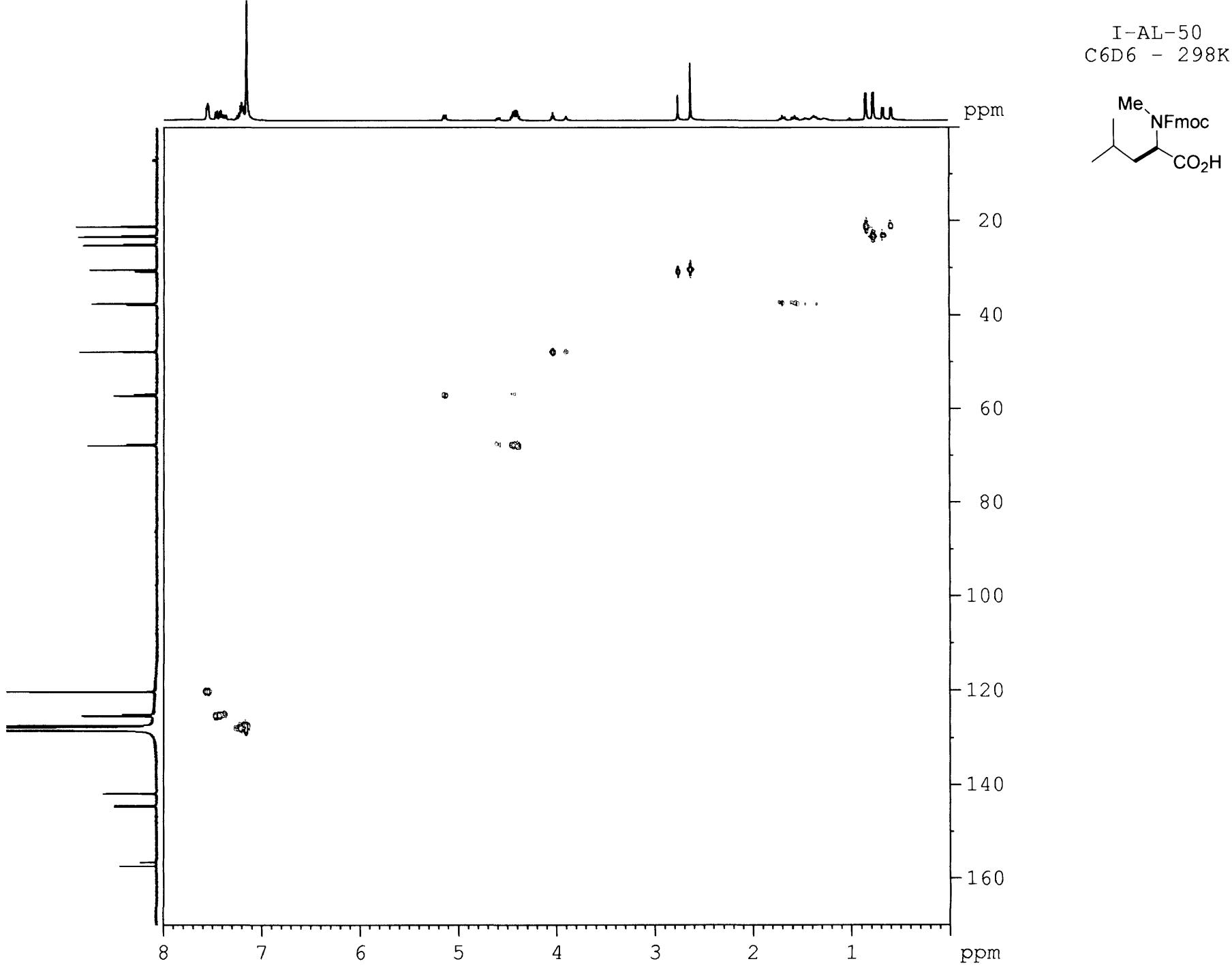


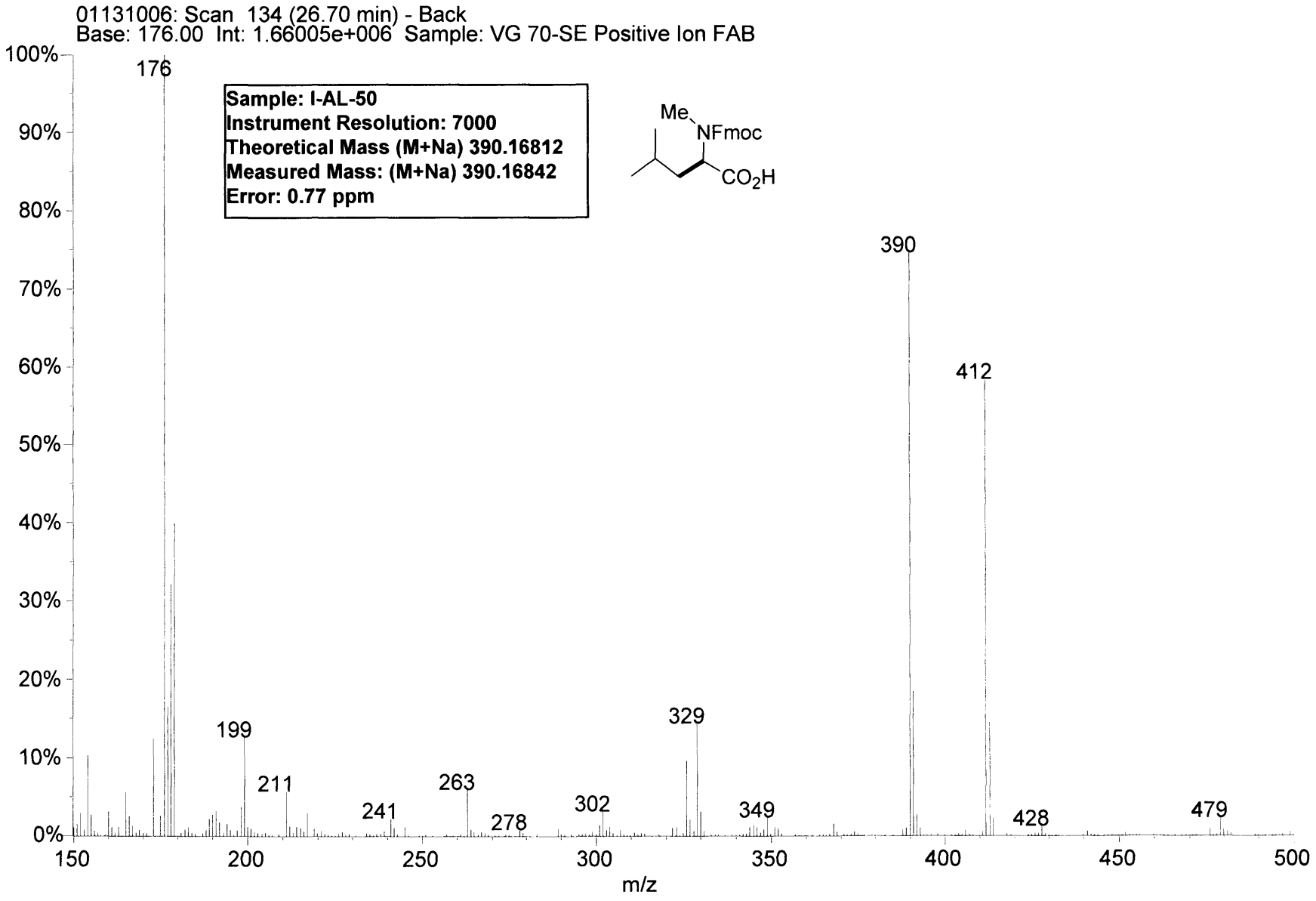
I-AL-50
C6D6 - 298K
13C

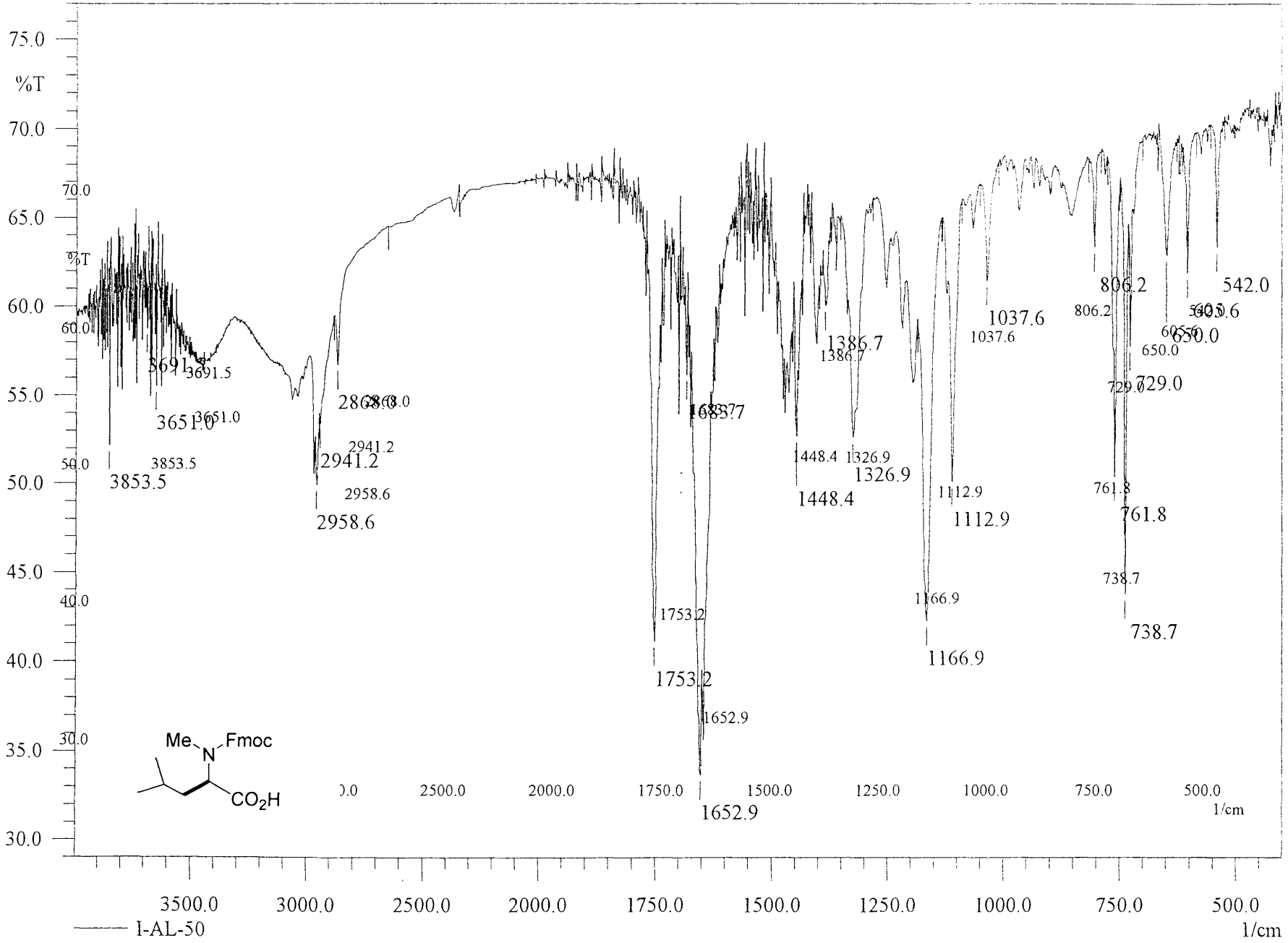




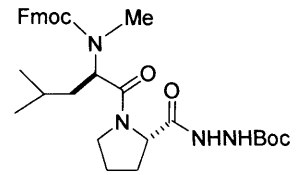
I-AL-50
C6D6 - 298K
COSY

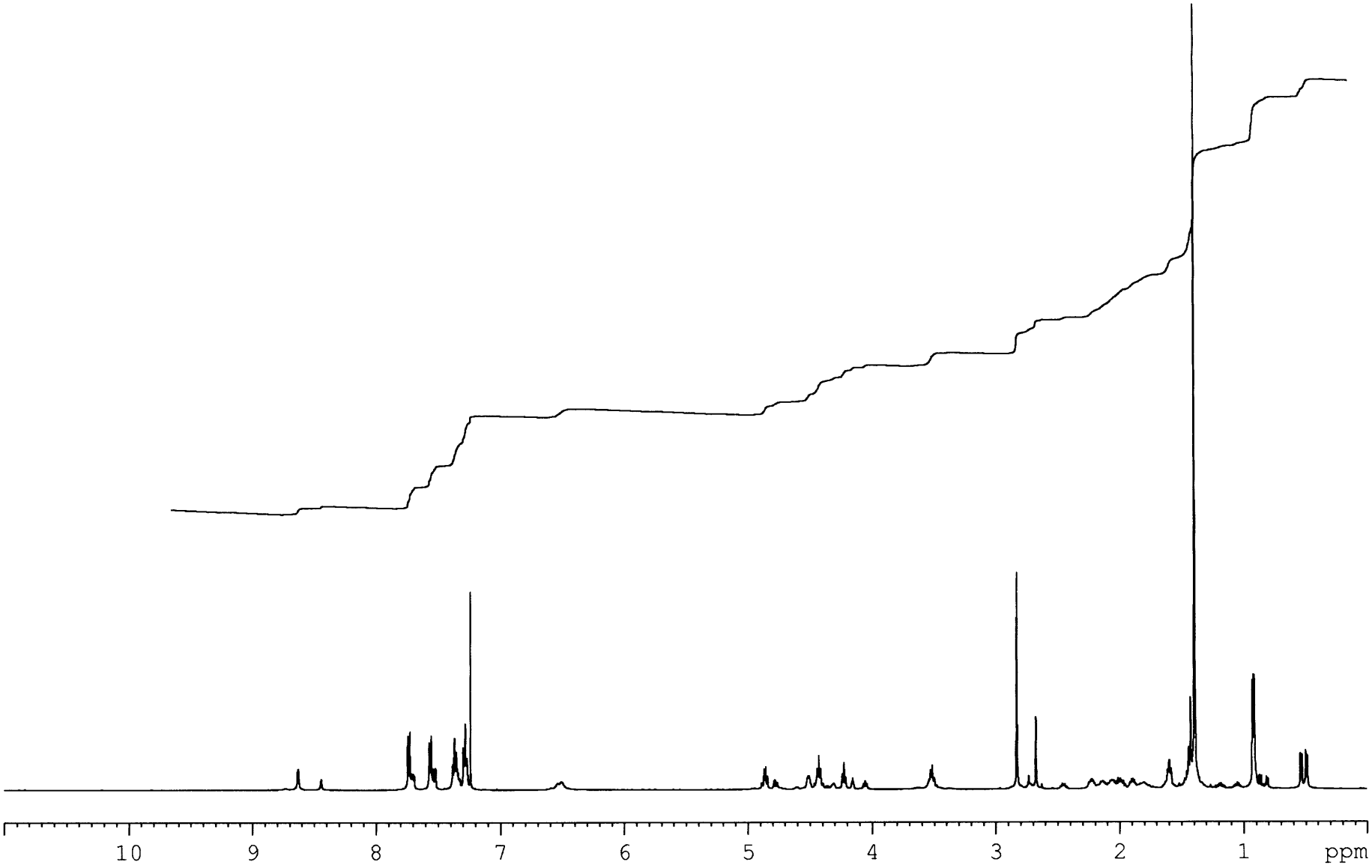

I-AL-50
C6D6 - 298K
Me
NFmoc
CO2H
ppm
20
40
60
80
100
120
140
160
8
7
6
5
4
3
2
1
ppm


01131006: Scan 134 (26.70 min) - Back
Base: 176.00 Int: 1.66005e+006 Sample: VG 70-SE Positive Ion FAB
Sample: I-AL-50
Instrument Resolution: 7000
Theoretical Mass (M+Na) 390.16812
Measured Mass: (M+Na) 390.16842
Error: 0.77 ppm
Me
NFmoc
CO2H
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
176
390
412
199
329
211
263
241
278
302
349
428
479
150
200
250
300
350
400
450
500
m/z

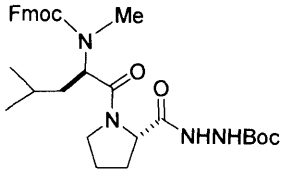

%T
1/cm
I-AL-50
Me
N
Fmoc
CO2H
3853.5
3691.5
3651.0
2941.2
2958.6
1753.2
1652.9
1448.4
1386.7
1326.9
1166.9
1112.9
1037.6
806.2
761.8
738.7
729.0
650.0
542.0

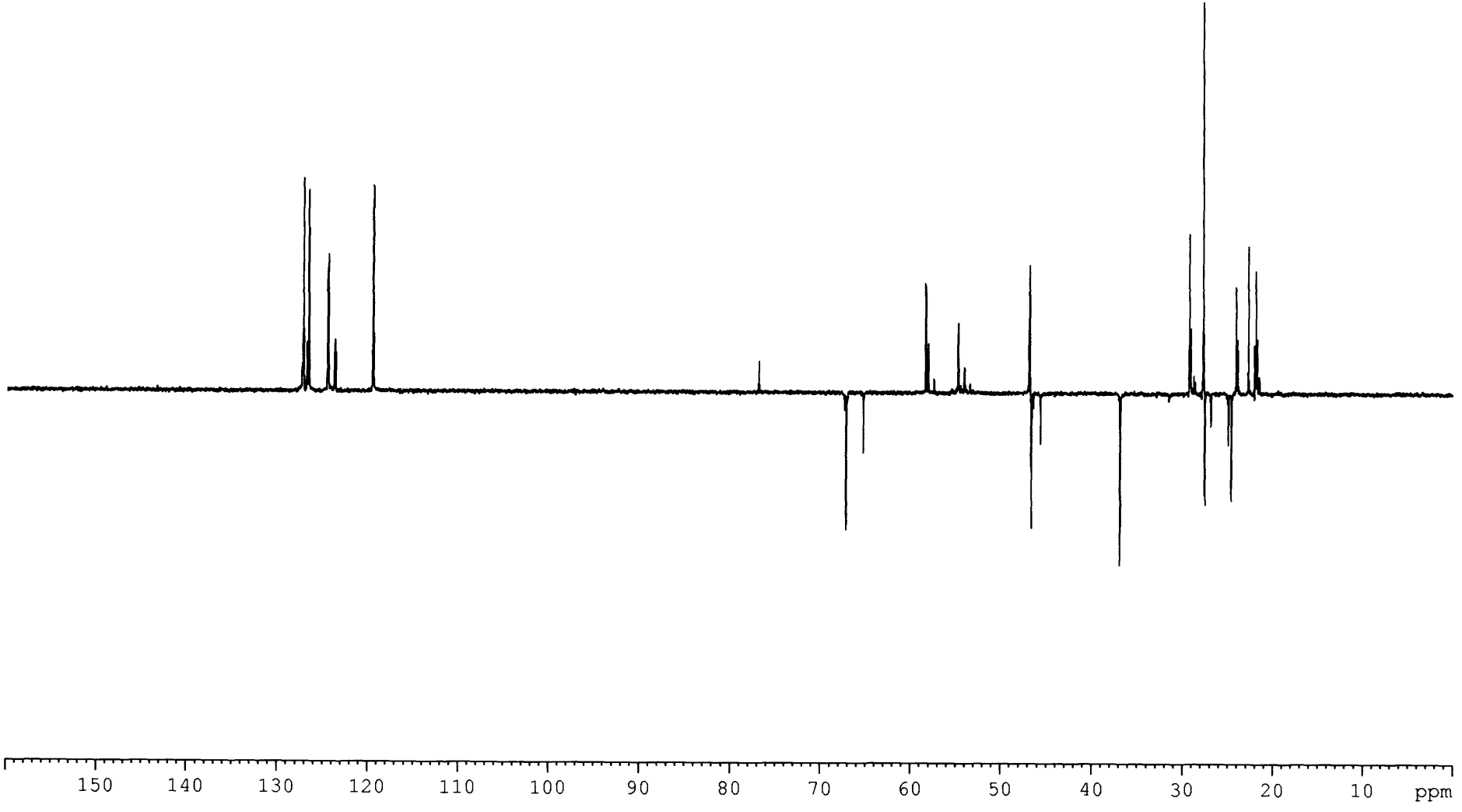
II-AL-106
CDCl3 - 298K



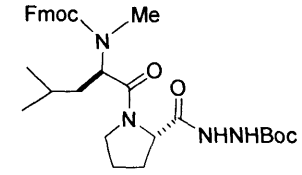


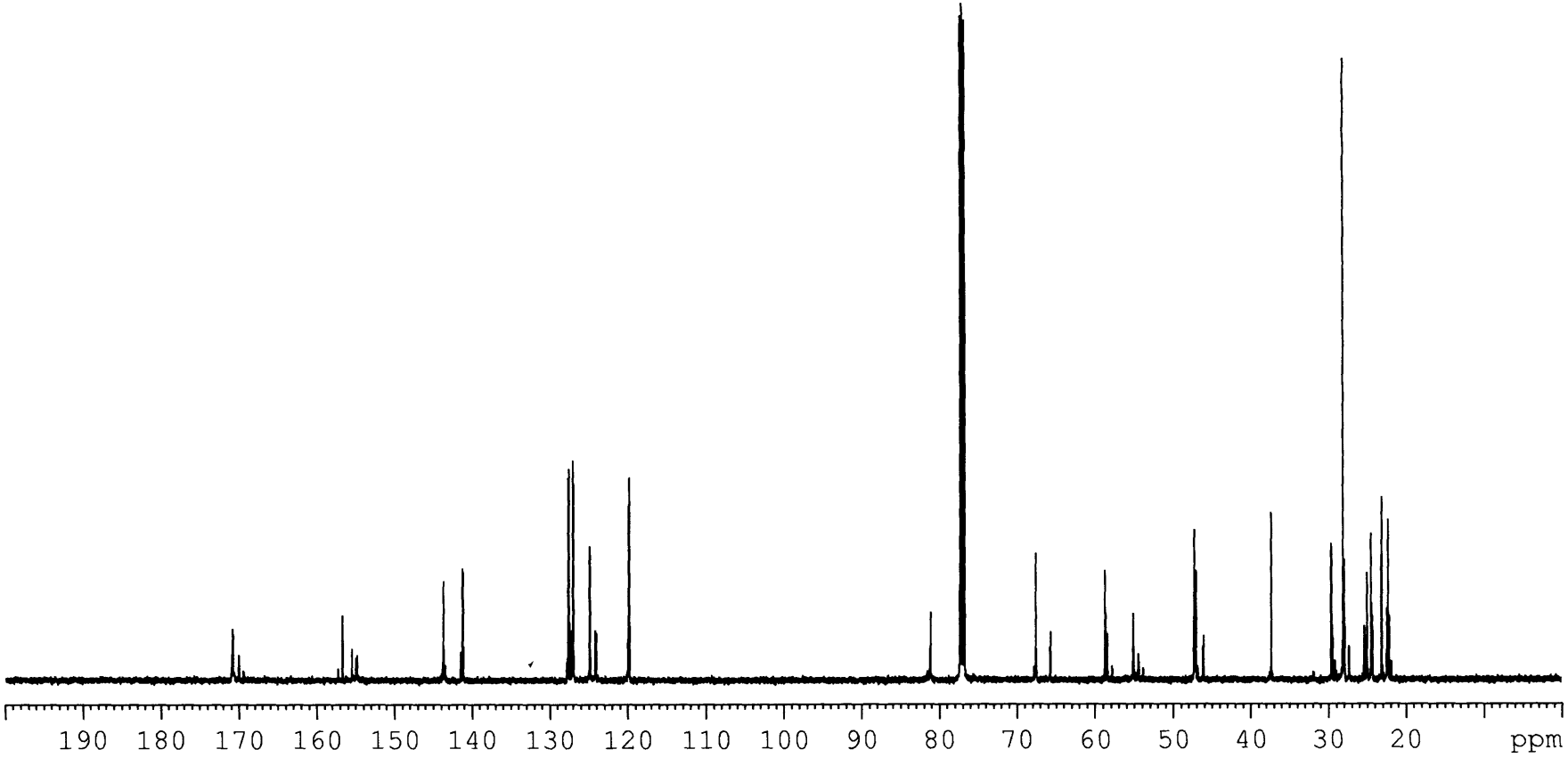
II-AL-106
DEPT
CDCL3 - 298K



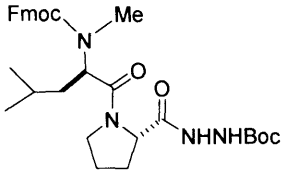


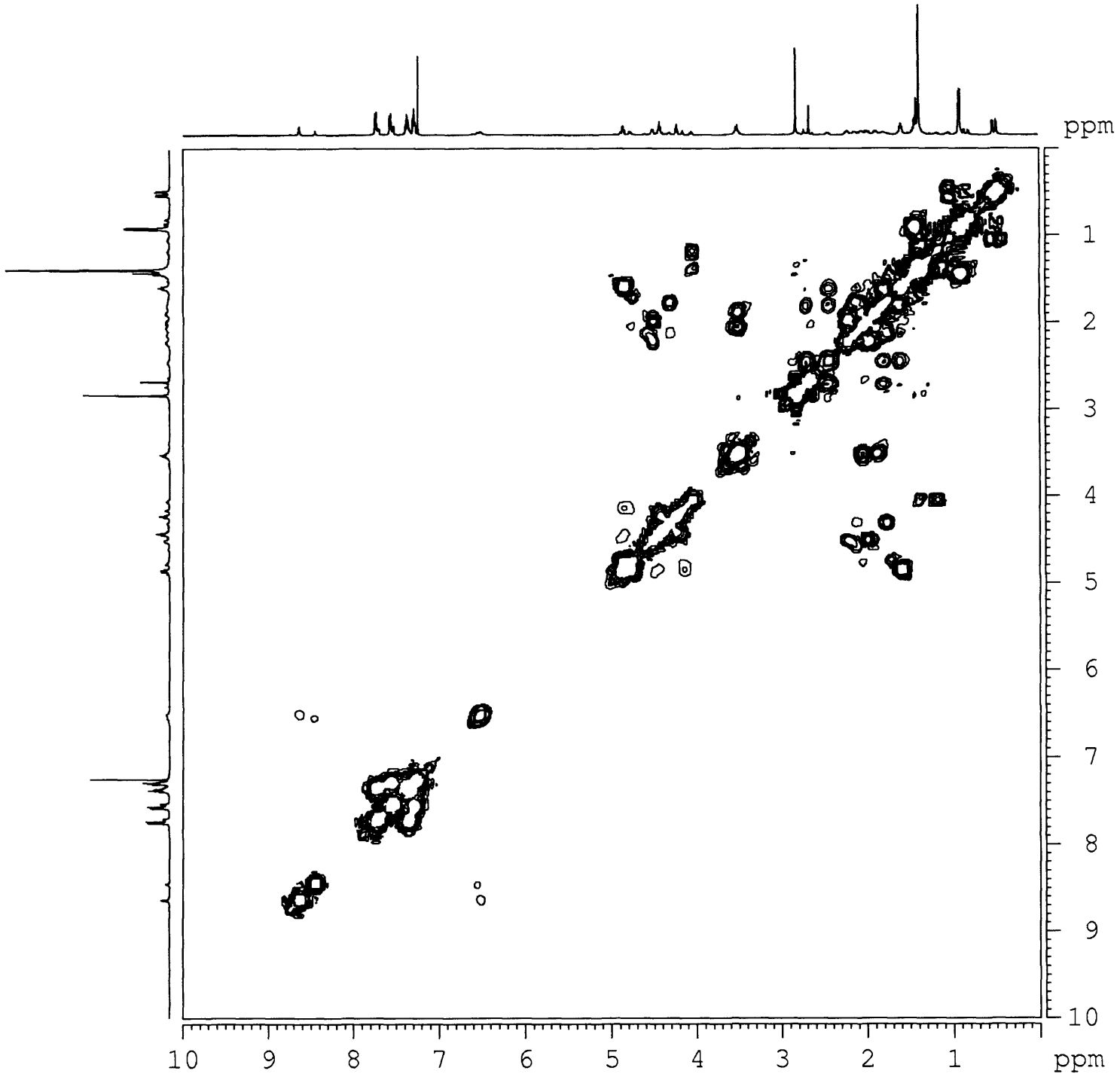
II-AL-106
13C
CDCl3 - 298K

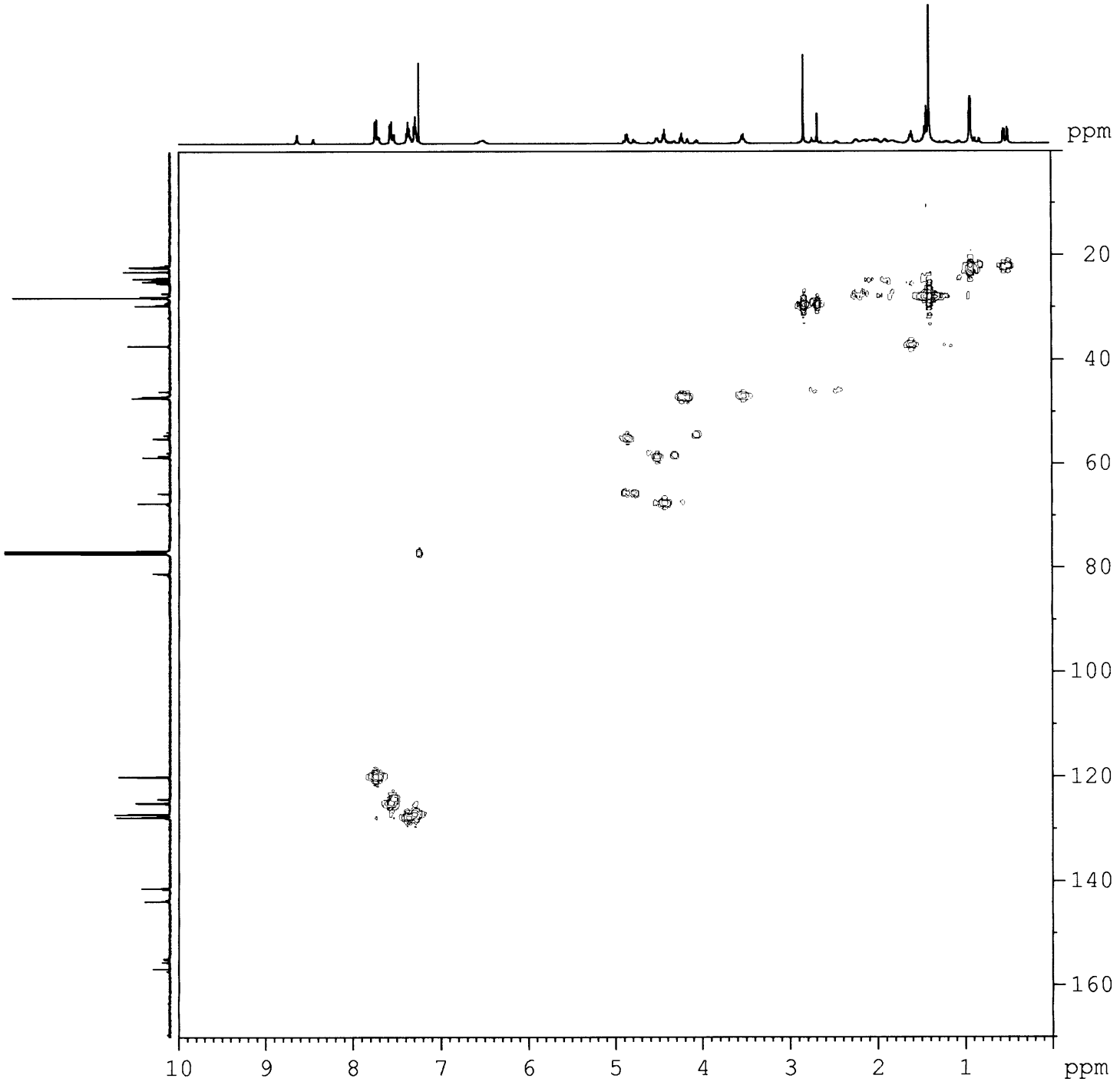




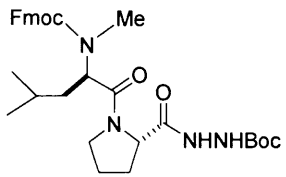
II-AL-106
COSY
CDCl3 - 298K

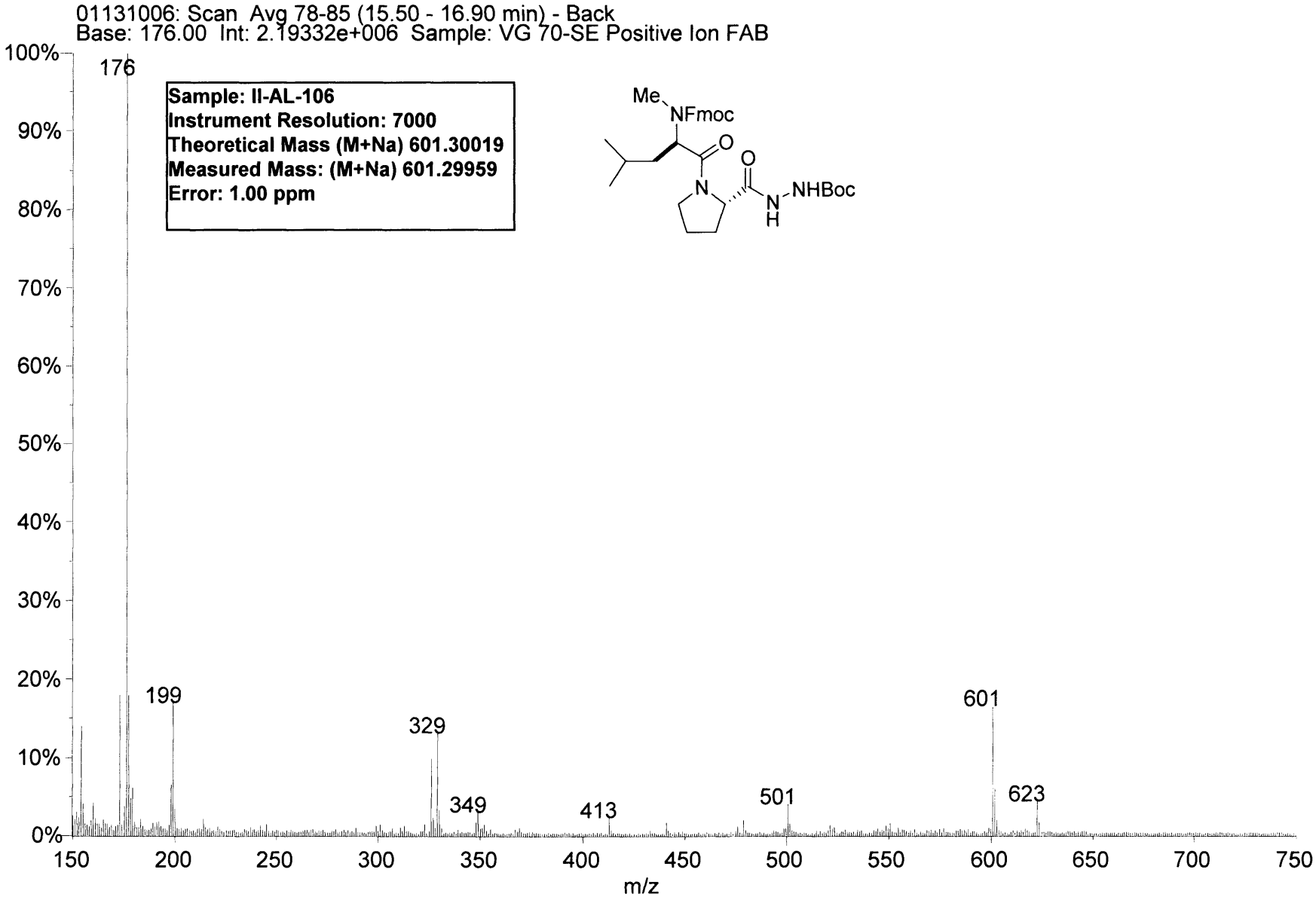


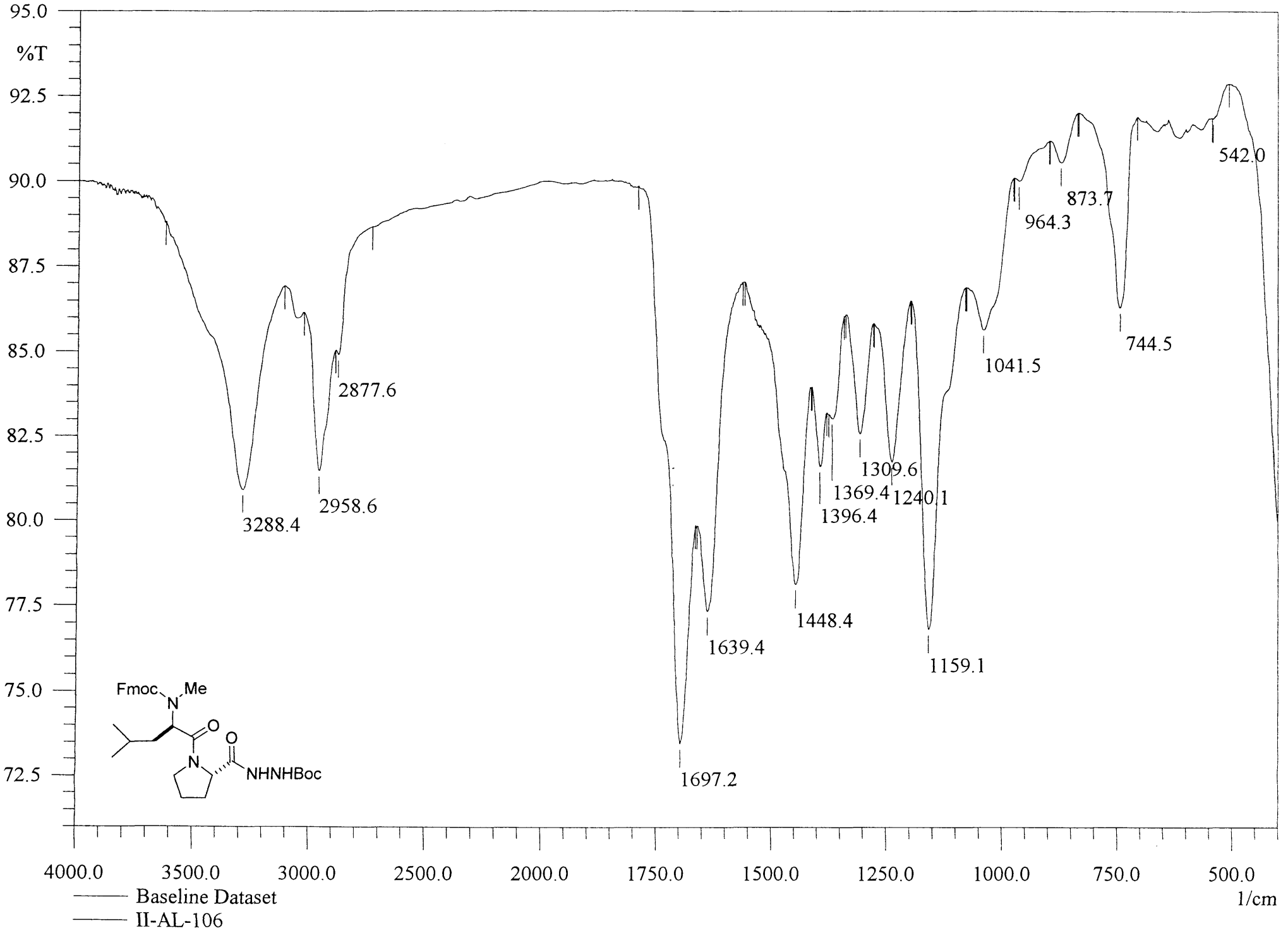




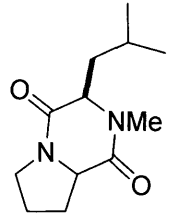
II-AL-106
HMQC
CDCl3 - 298K



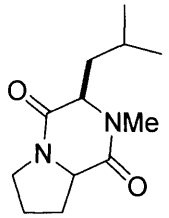

01131006: Scan Avg 78-85 (15.50 - 16.90 min) - Back
Base: 176.00 Int: 2.19332e+006 Sample: VG 70-SE Positive Ion FAB
Sample: II-AL-106
Instrument Resolution: 7000
Theoretical Mass (M+Na) 601.30019
Measured Mass: (M+Na) 601.29959
Error: 1.00 ppm
Me
NFmoc
O
O
N
N
H
NHBoc
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
176
199
329
349
413
501
601
623
150
200
250
300
350
400
450
500
550
600
650
700
750
m/z


95.0
%T
92.5
90.0
87.5
85.0
82.5
80.0
77.5
75.0
72.5
3288.4
2958.6
2877.6
1697.2
1639.4
1448.4
1396.4
1369.4
1309.6
1240.1
1159.1
1041.5
964.3
873.7
744.5
542.0
Fmoc
N
Me
O
O
N
NHNHBoc
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
Baseline Dataset
II-AL-106

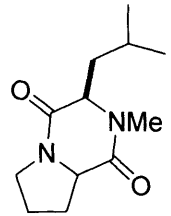
I-AL-65ws
cyclisation product
CDCl3 - 298K

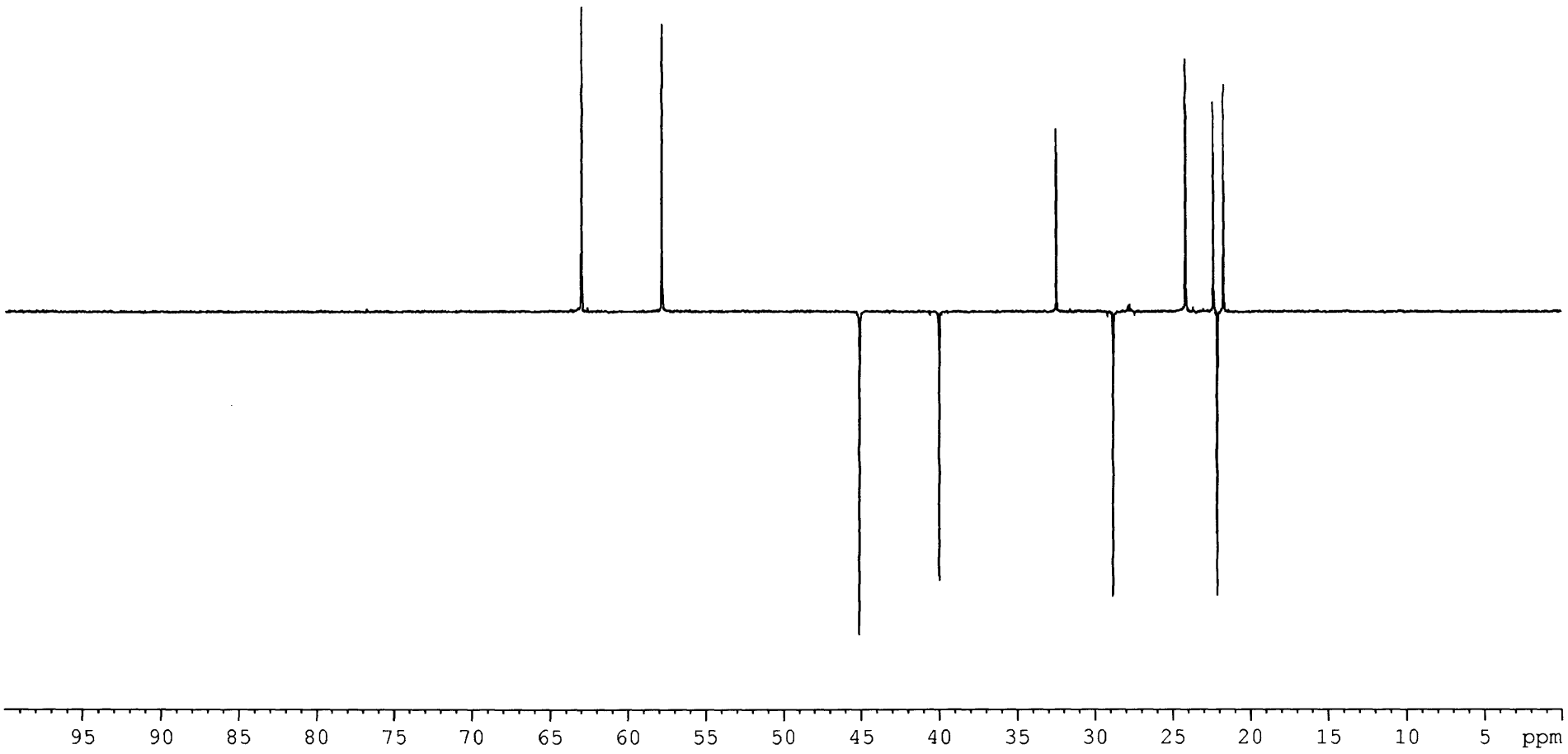


I-AL-65ws
cyclisation product
CDCl3 - 298K

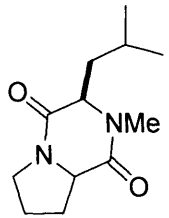


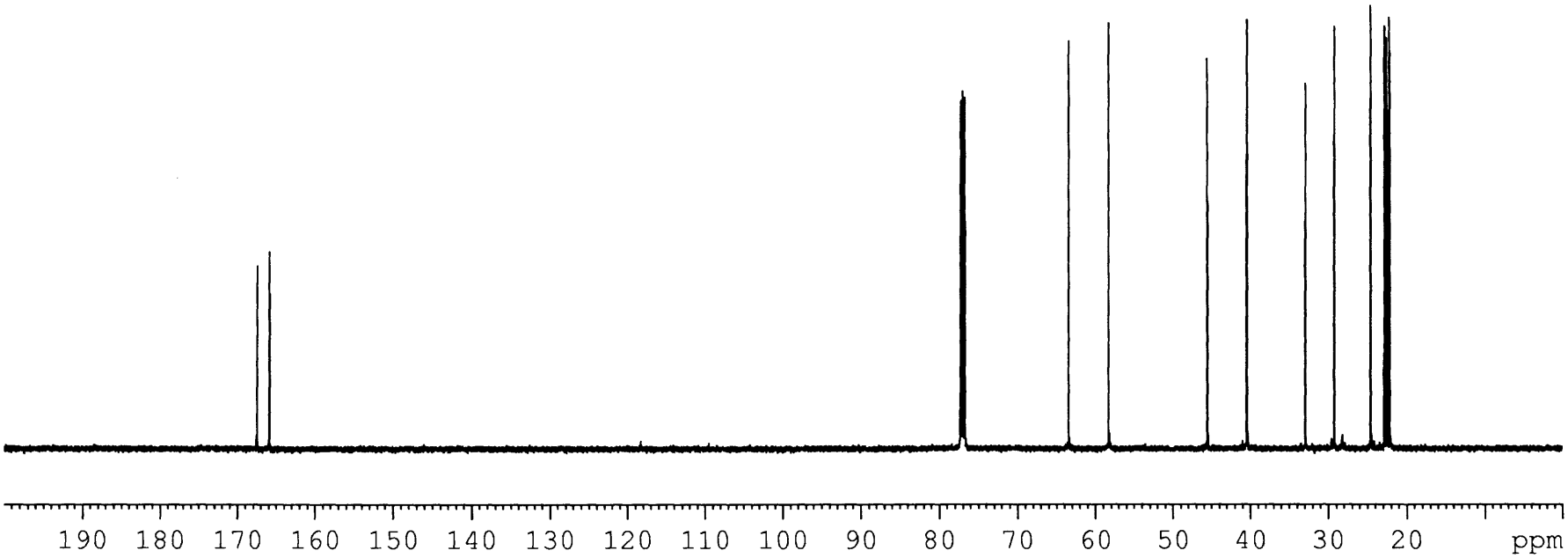
I-AL-65ws
CDCL3 - 298K
DEPT

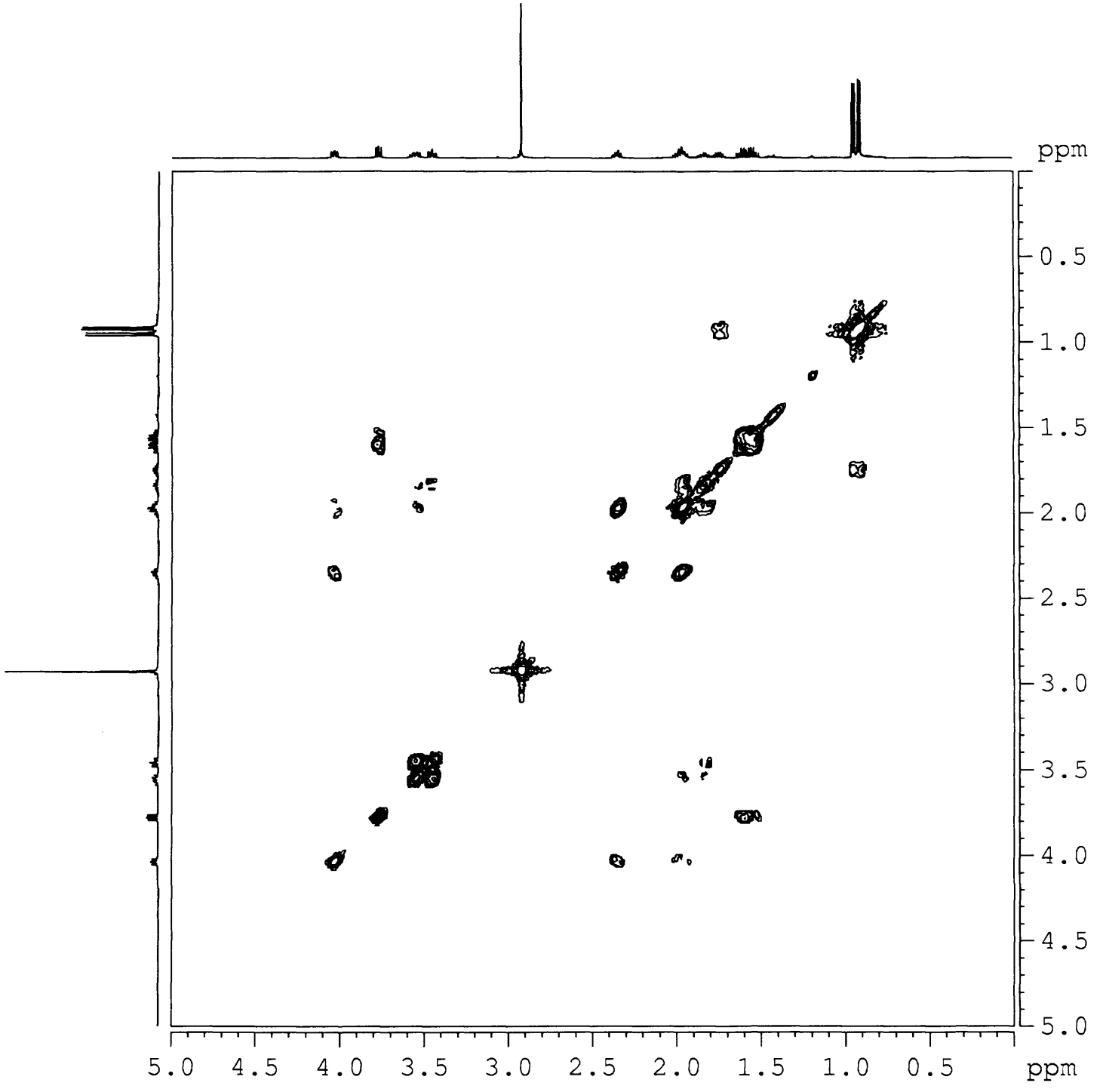




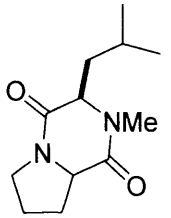
I-AL-65ws
CDCL3 - 298K
13C





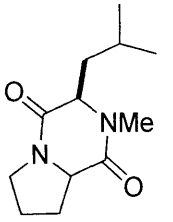


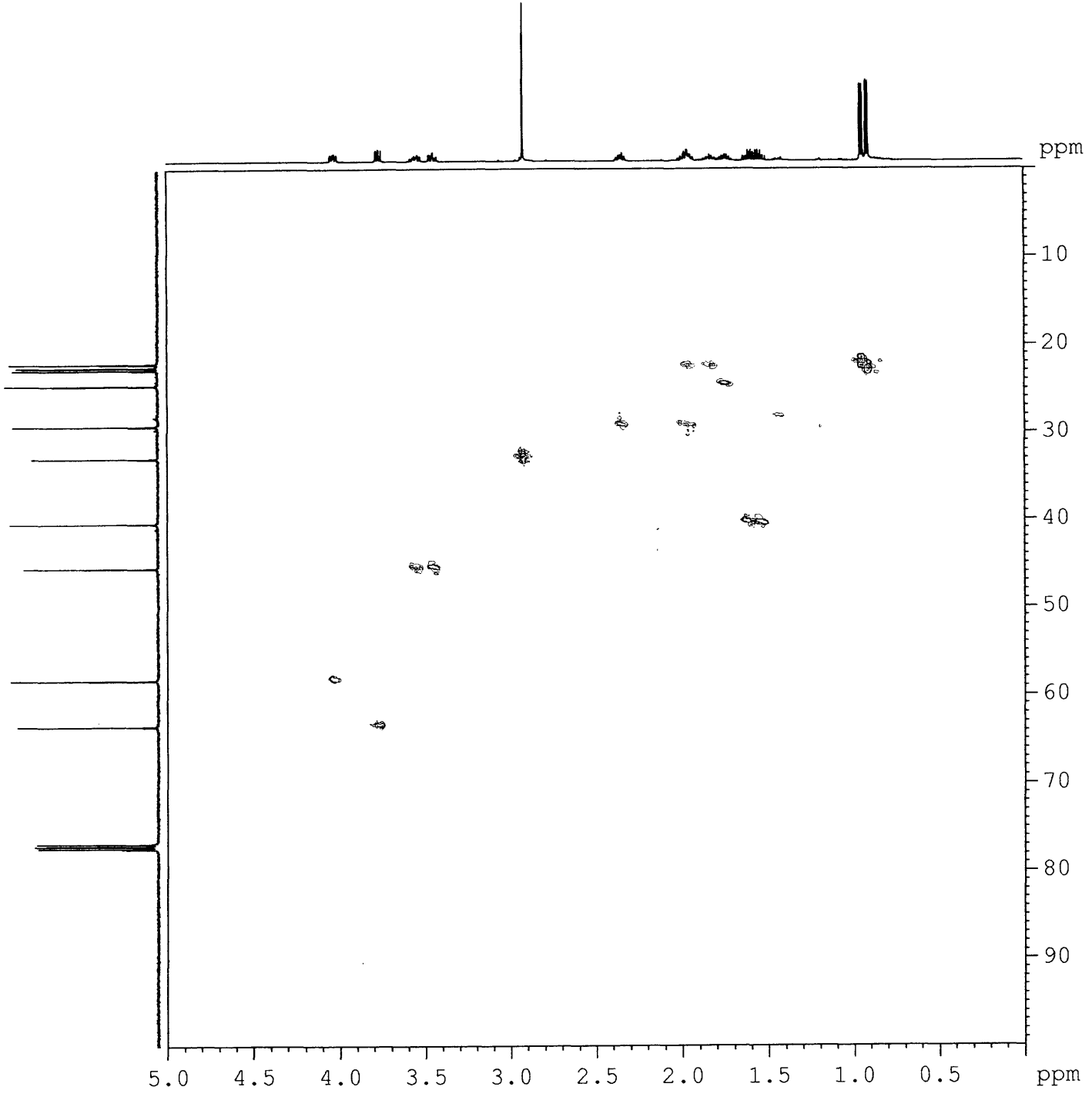
I-AL-65ws
CDCL3 - 298K
COSY

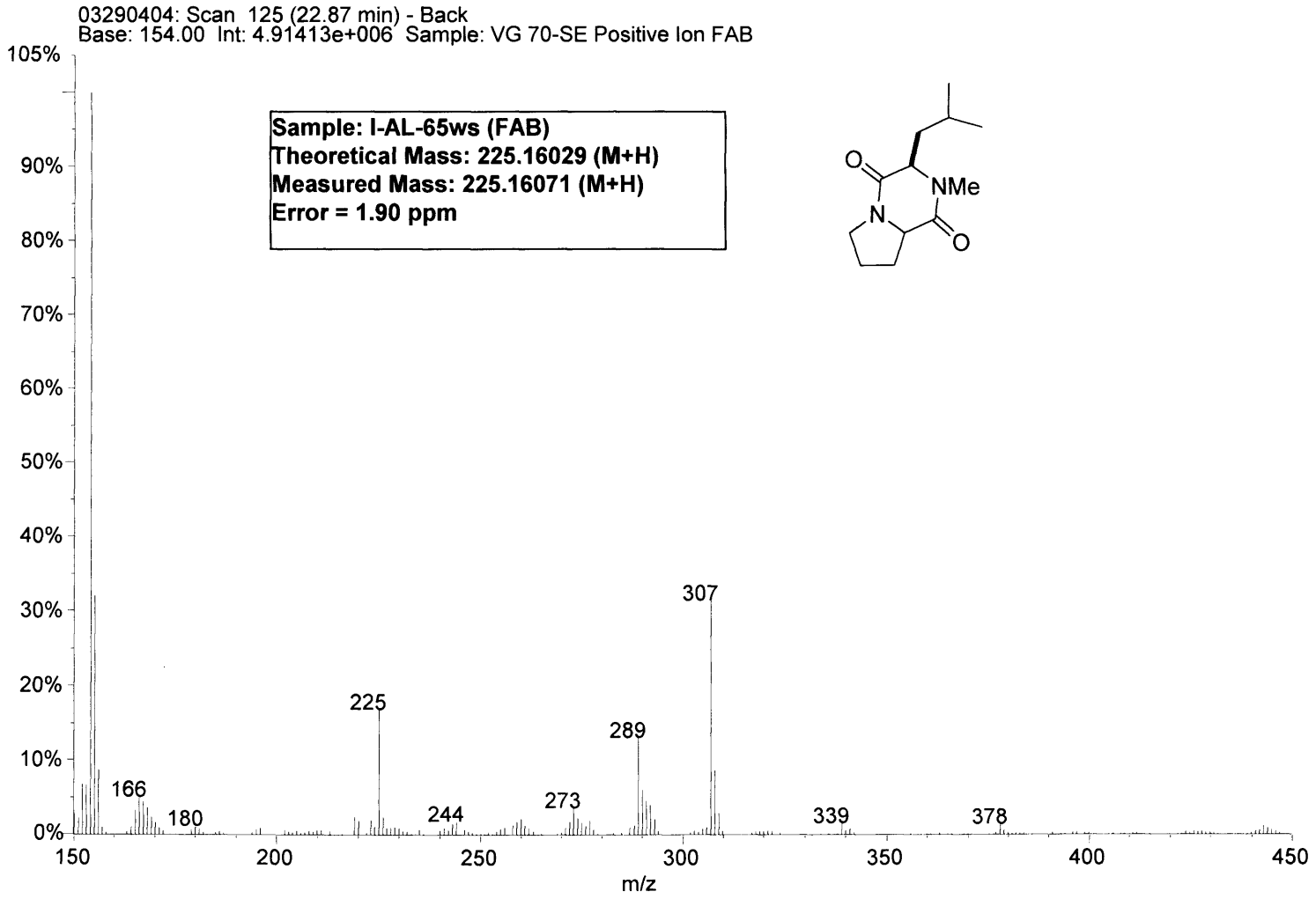


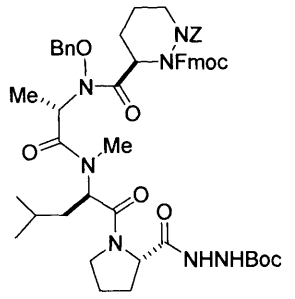
I-AL-65ws
CDCL3 - 298K

HMQC



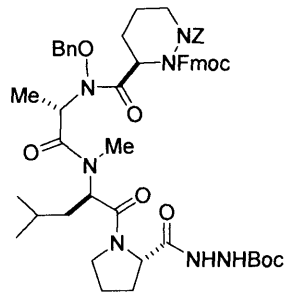


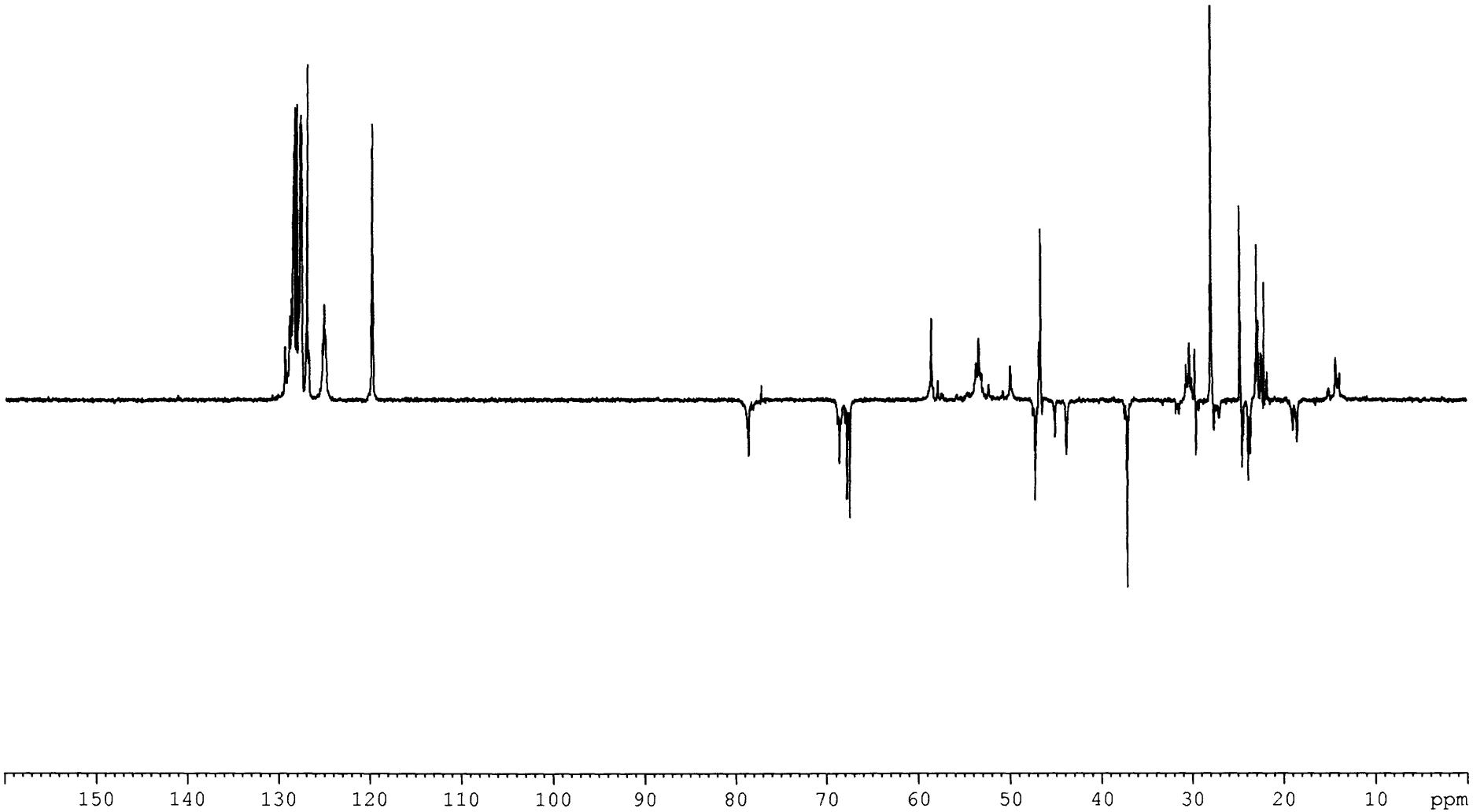

03290404: Scan 125 (22.87 min) - Back
Base: 154.00 Int: 4.91413e+006 Sample: VG 70-SE Positive Ion FAB
Sample: I-AL-65ws (FAB)
Theoretical Mass: 225.16029 (M+H)
Measured Mass: 225.16071 (M+H)
Error = 1.90 ppm
O
NMe
N
O
105%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
307
225
289
166
180
244
273
339
378
150
200
250
300
350
400
450
m/z

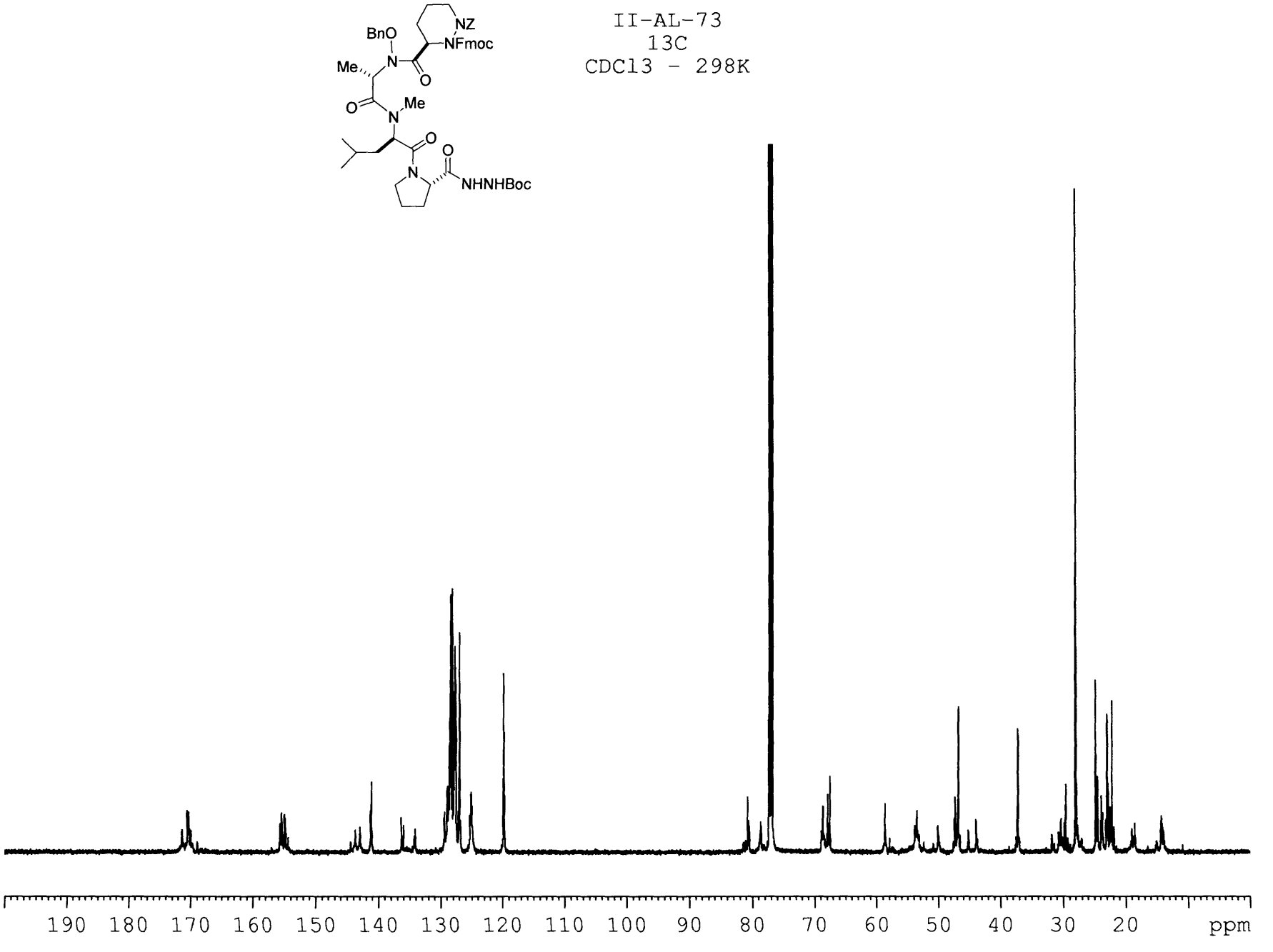


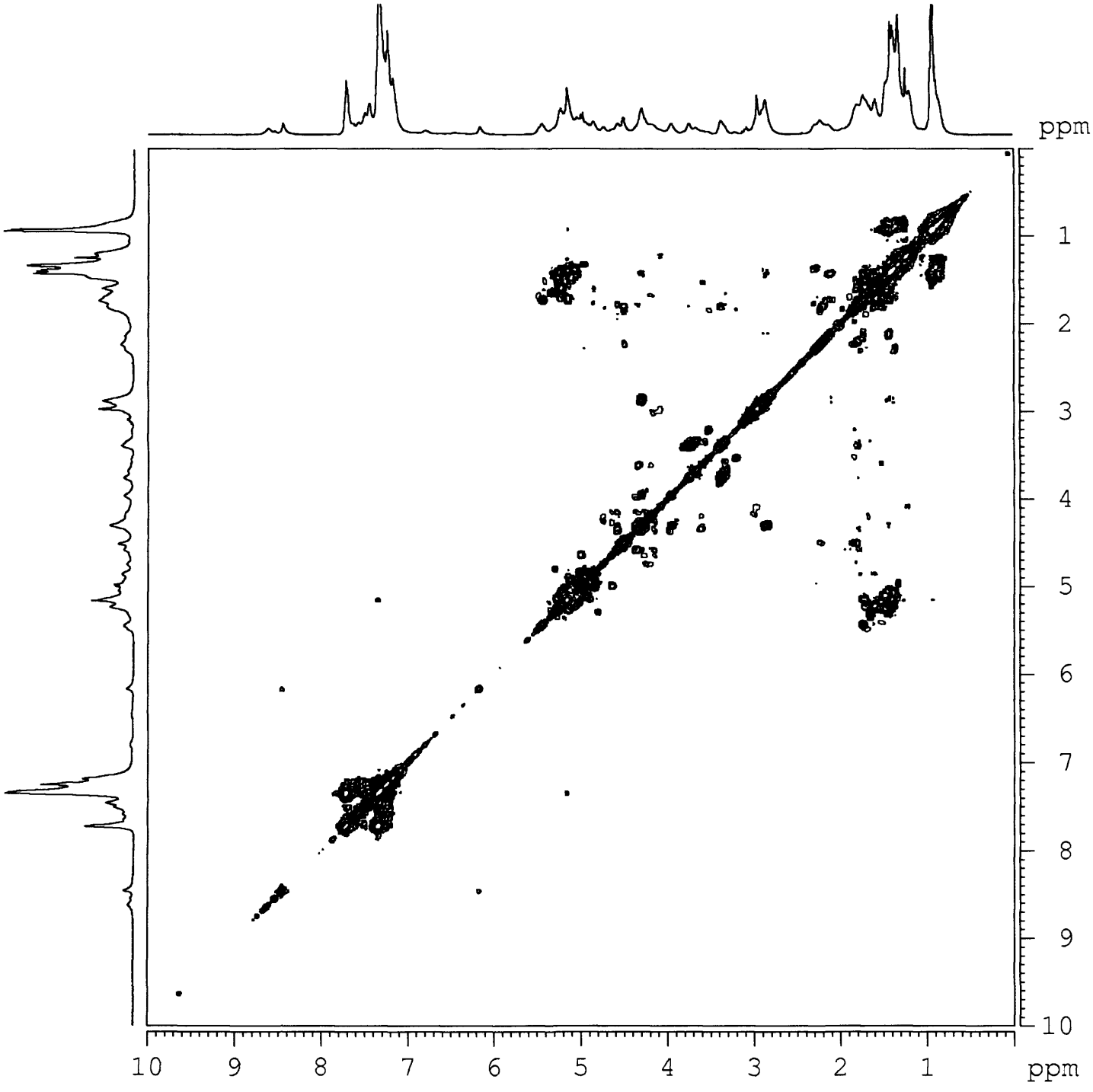
II-AL-73
CDCl3 - 298K

II-AL-73
DEPT
CDCl3 - 298K

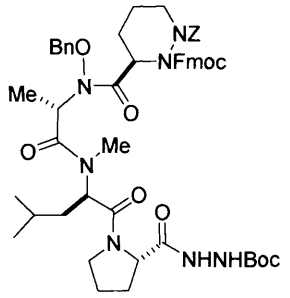


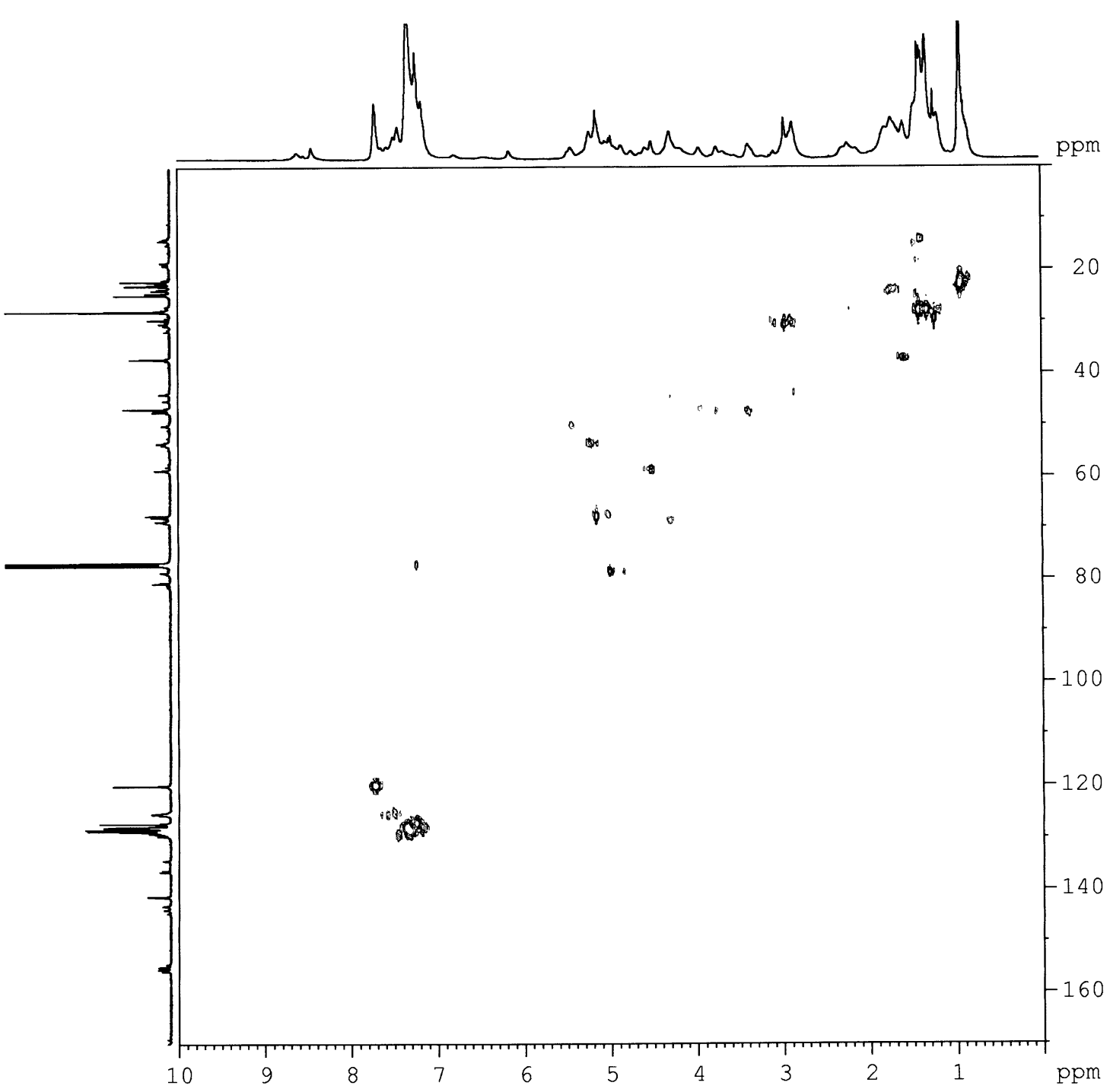



BnO
N
Me
O
N
Me
O
O
N
NZ
NFmoc
O
N
O
NHNHBoc
II-AL-73
13C
CDCl3 - 298K
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

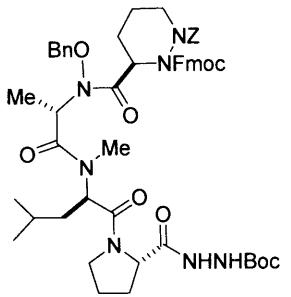


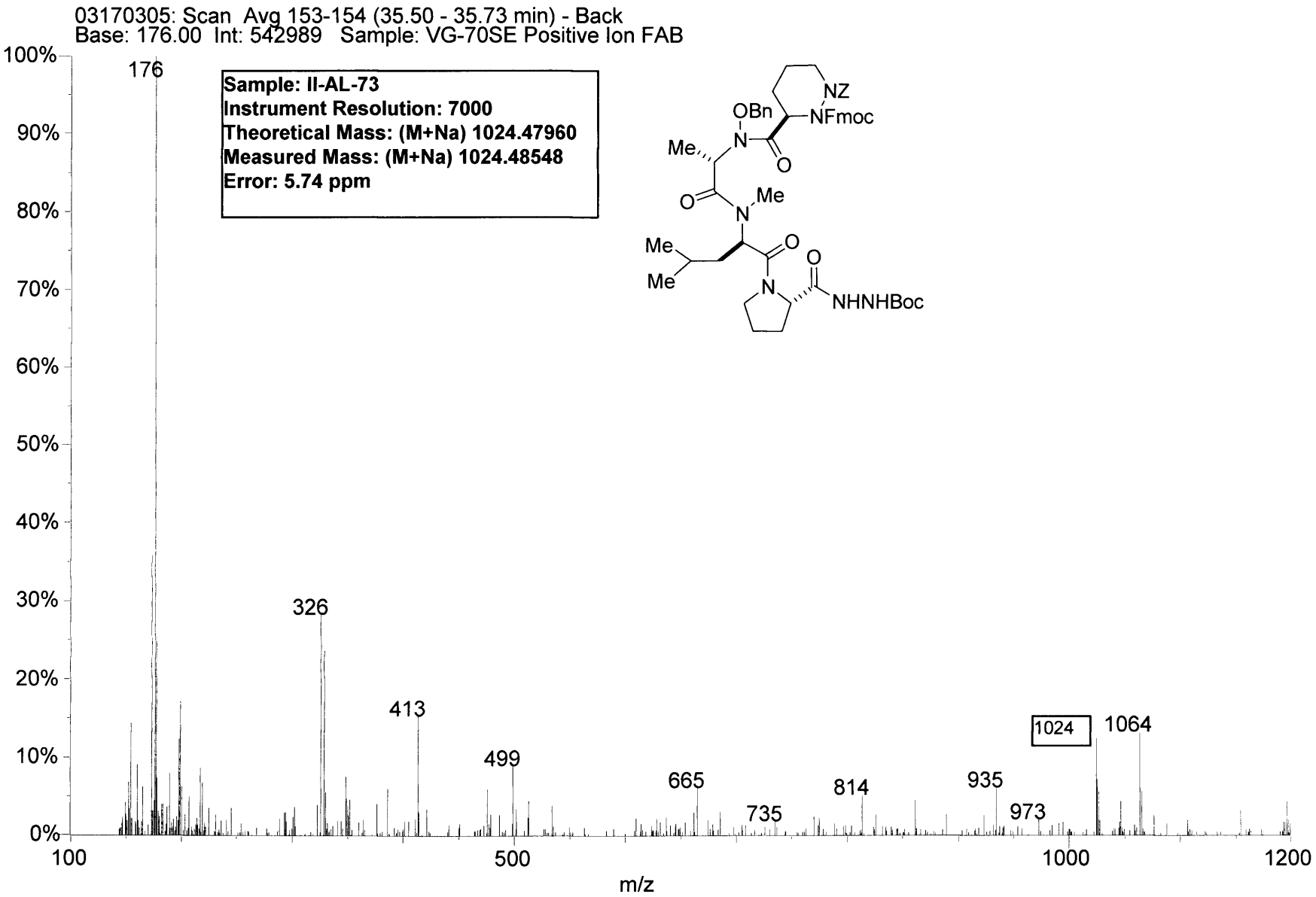
II-AL-73
cosy
CDCl3 - 298K

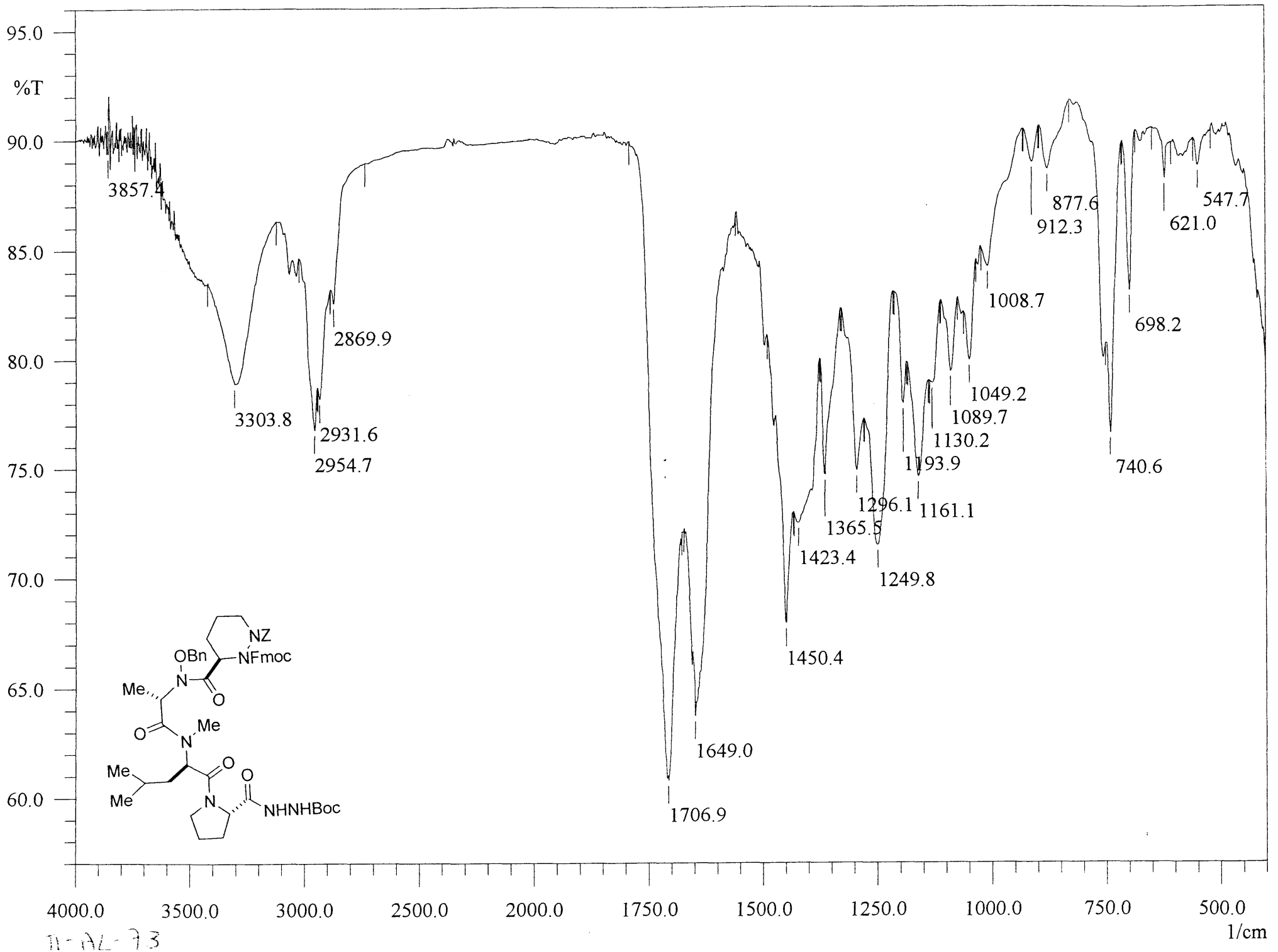




II-AL-73
HMQC
CDC3 - 298K

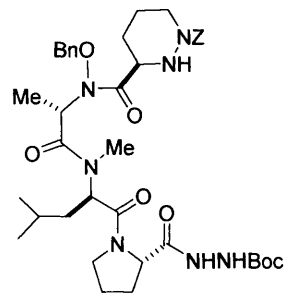


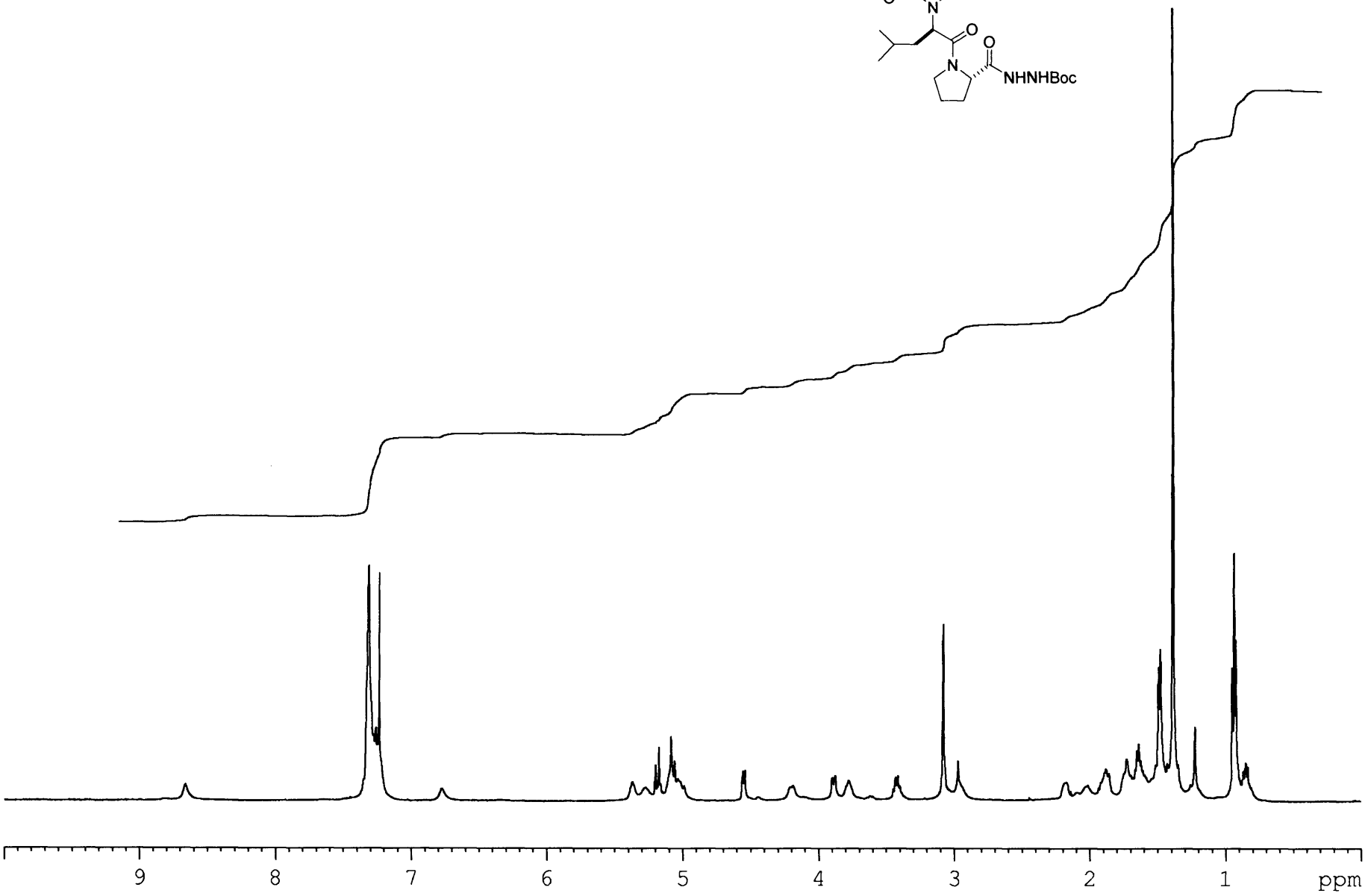

03170305: Scan Avg 153-154 (35.50 - 35.73 min) - Back
Base: 176.00 Int: 542989 Sample: VG-70SE Positive Ion FAB
Sample: II-AL-73
Instrument Resolution: 7000
Theoretical Mass: (M+Na) 1024.47960
Measured Mass: (M+Na) 1024.48548
Error: 5.74 ppm
NZ
NFmoc
OBn
Me
Me
Me
NHNHBoc
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
176
326
413
499
665
735
814
935
973
1024
1064
100
500
1000
1200
m/z


95.0
%T
90.0
85.0
80.0
75.0
70.0
65.0
60.0
3857.4
3303.8
2869.9
2931.6
2954.7
1706.9
1649.0
1450.4
1423.4
1365.5
1296.1
1249.8
1193.9
1161.1
1130.2
1089.7
1049.2
1008.7
912.3
877.6
740.6
698.2
621.0
547.7
NZ
NFmoc
OBn
N
O
Me
Me
N
Me
O
O
Me
Me
O
N
NHNHBoc
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm

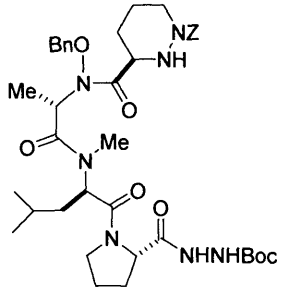
11-AL-73

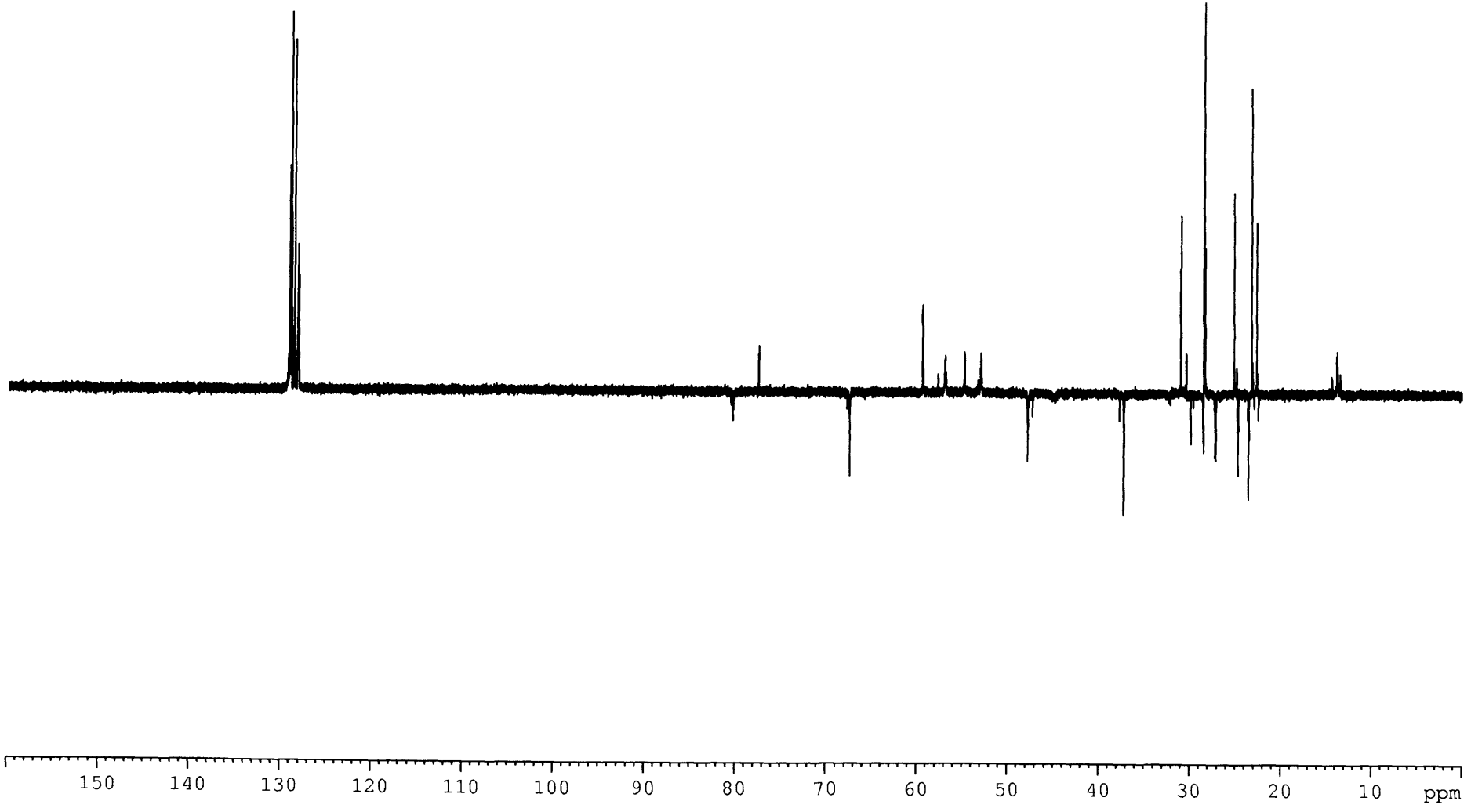
II-AL-72
CDCl3 - 298K



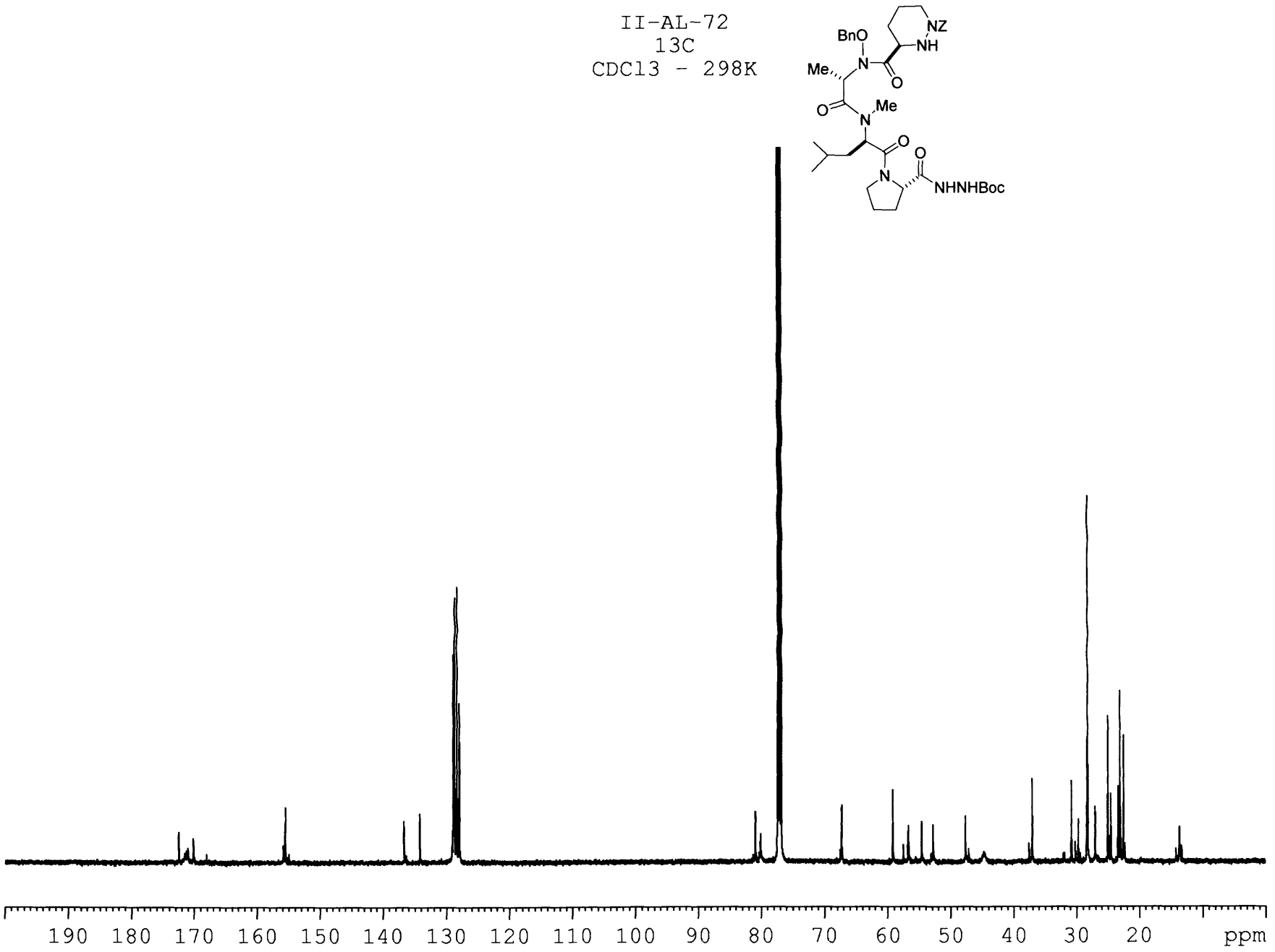


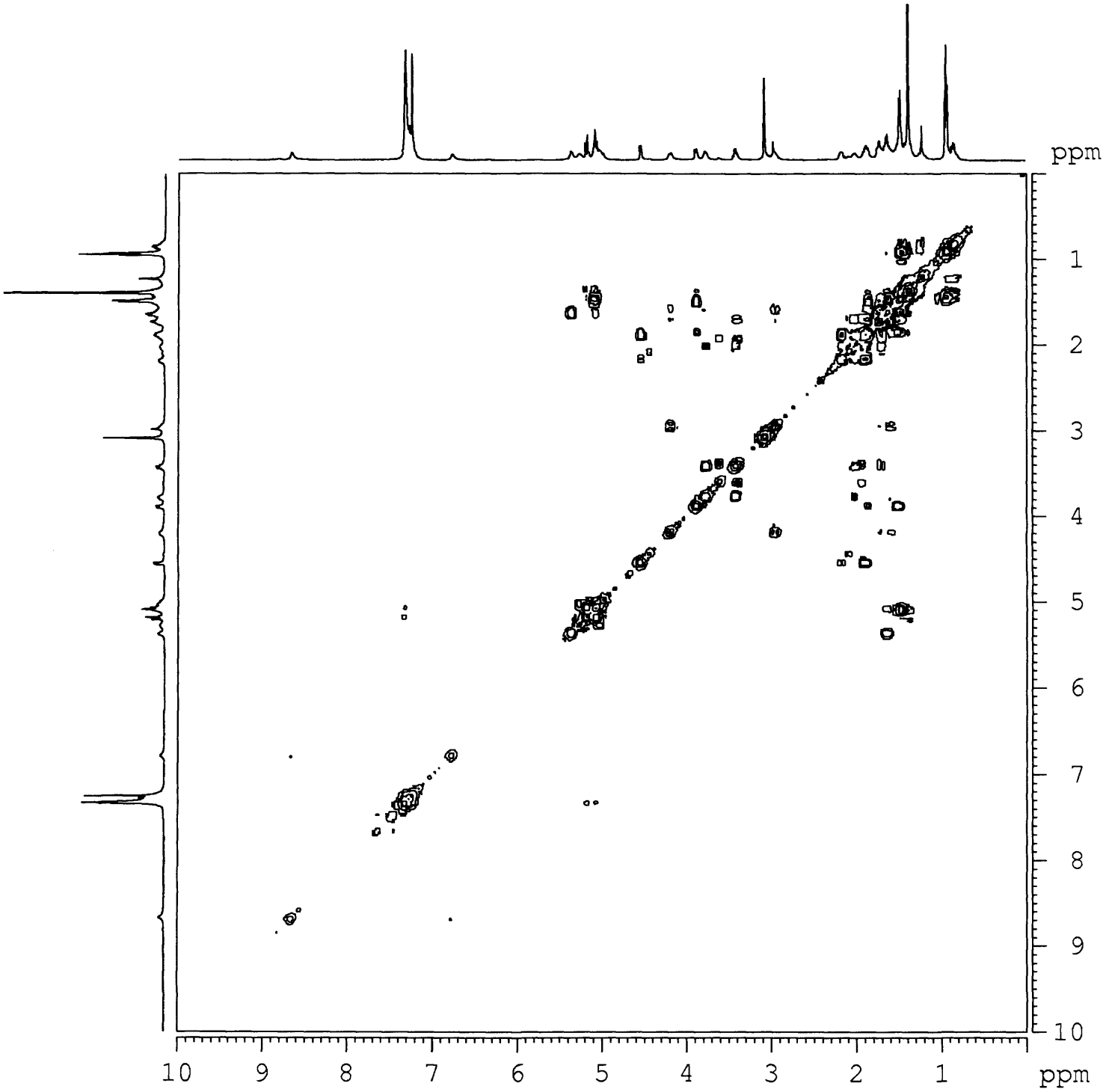
II-AL-72
DEPT
CDCl3 - 298K



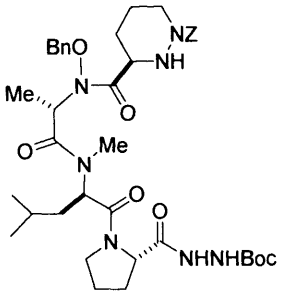


II-AL-72
13C
CDCl3 - 298K

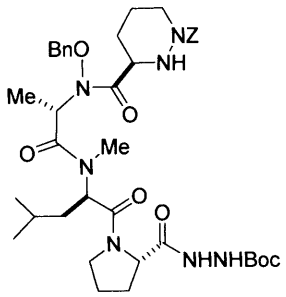


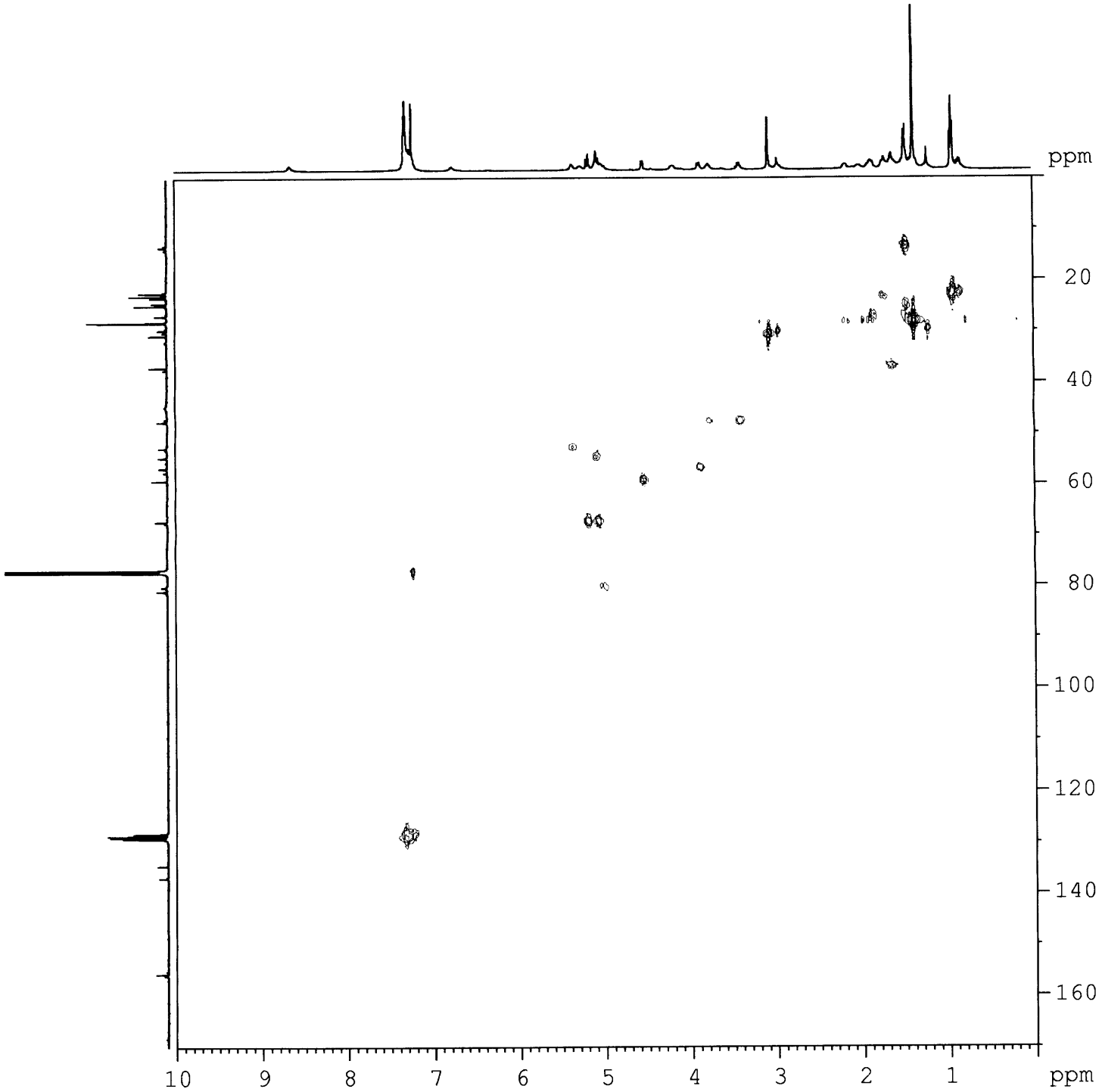


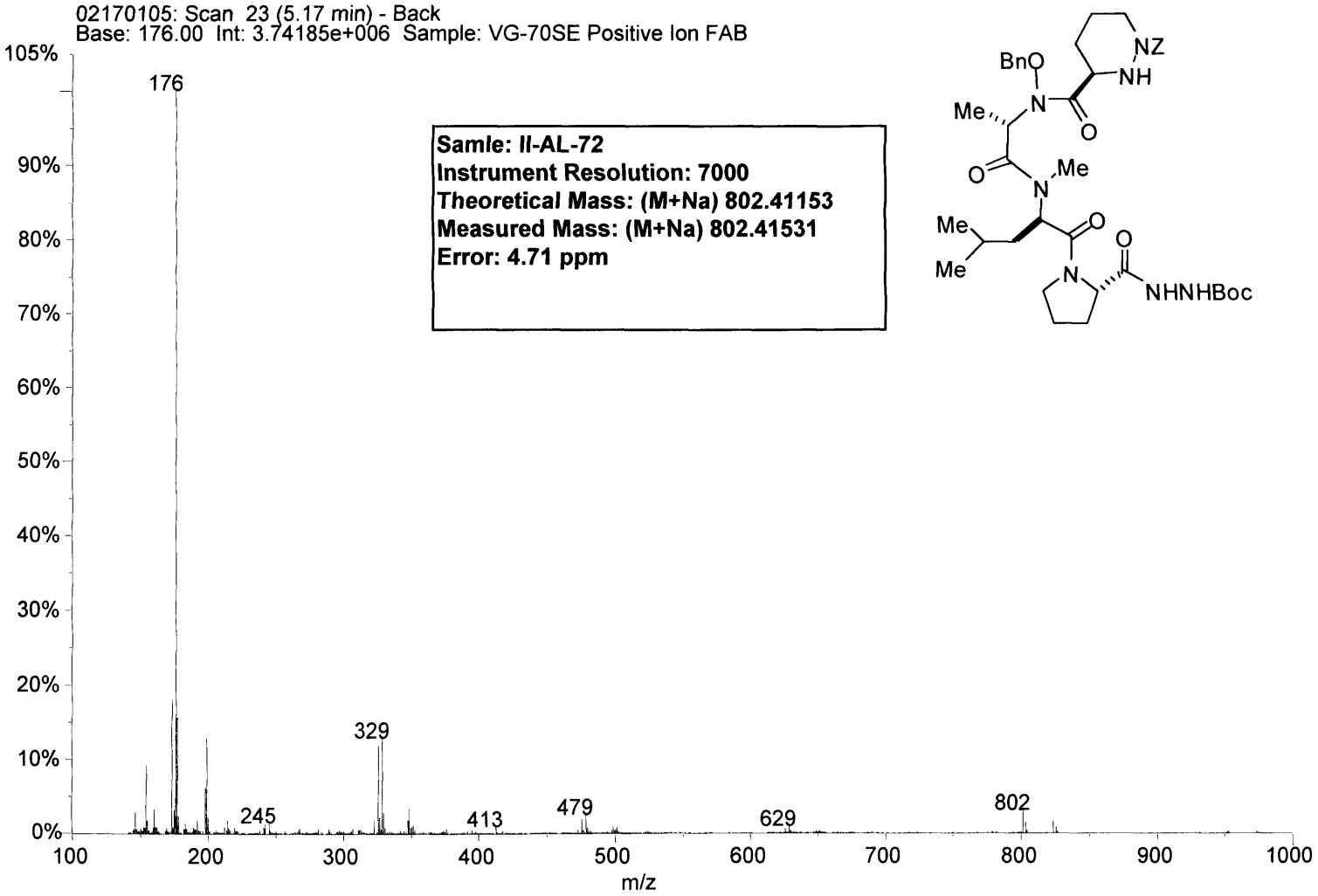
II-AL-72
COSY
CDCl3 - 298K
500 MHz

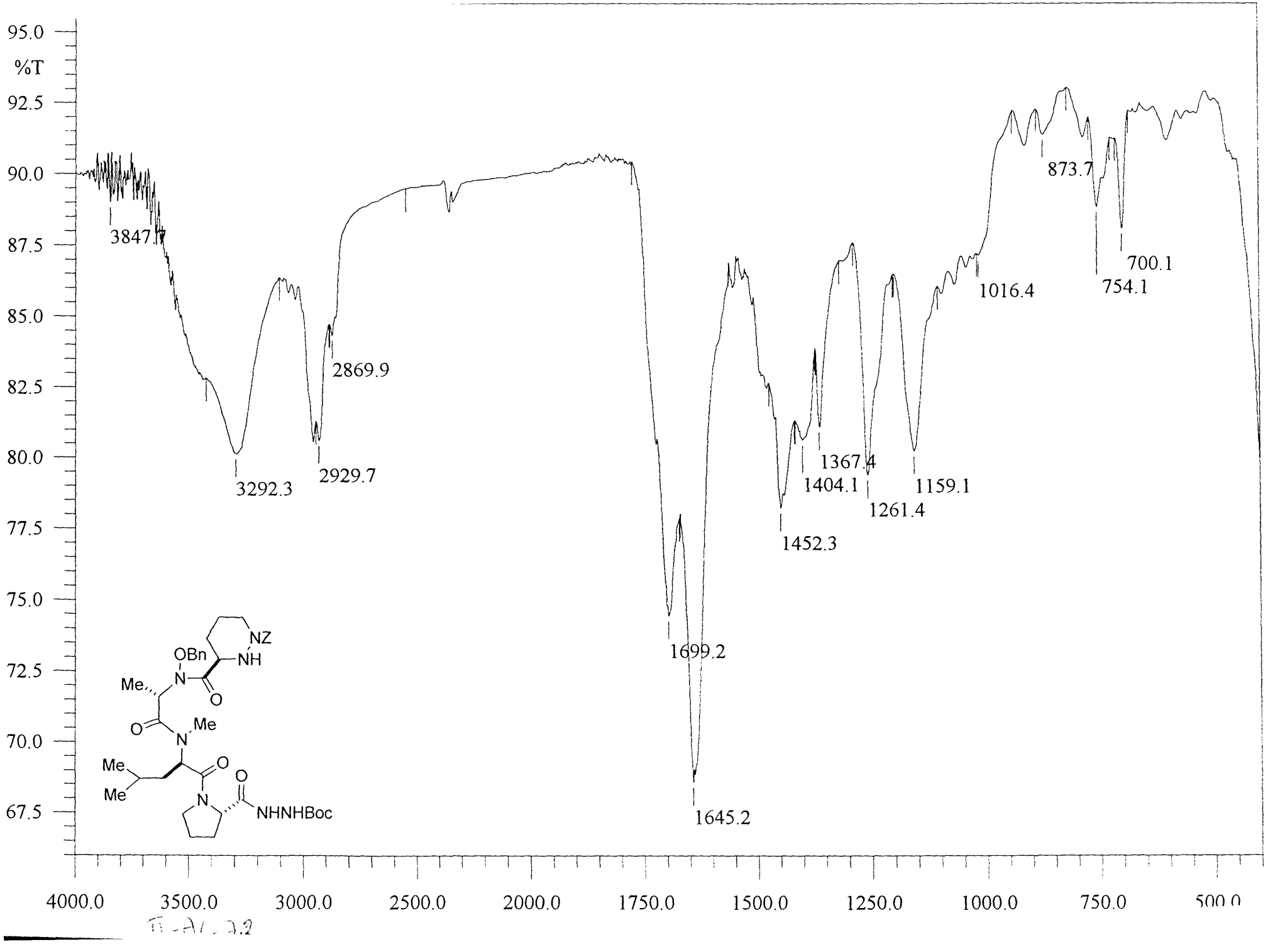


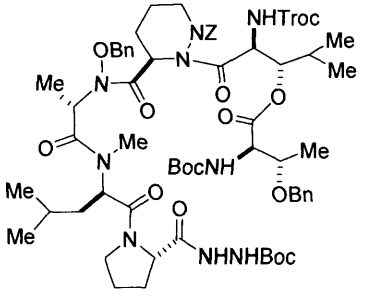
II-AL-72
HMQC
CDCl3 - 298K
500 MHz



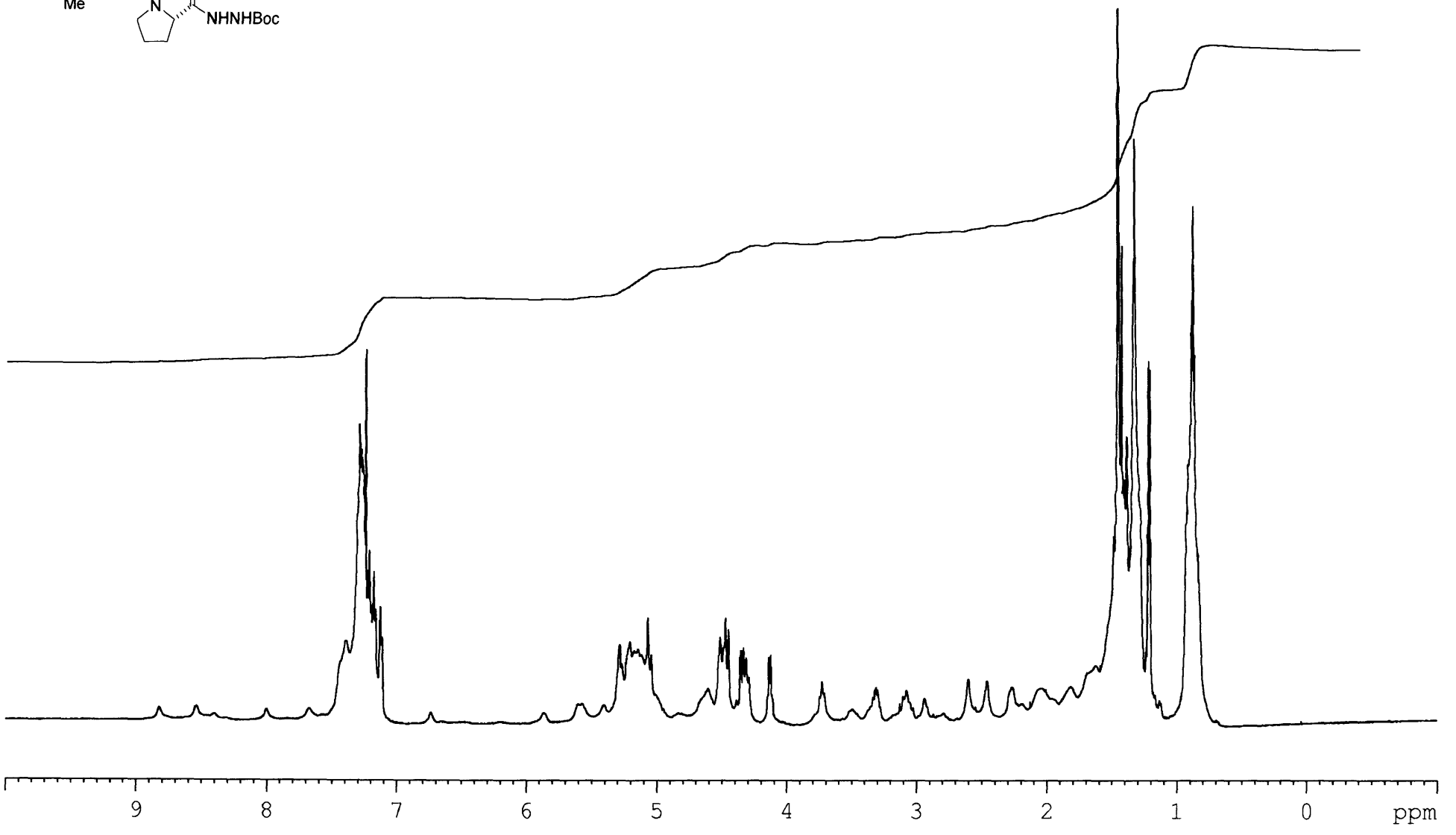



02170105: Scan 23 (5.17 min) - Back
Base: 176.00 Int: 3.74185e+006 Sample: VG-70SE Positive Ion FAB
Samle: II-AL-72
Instrument Resolution: 7000
Theoretical Mass: (M+Na) 802.41153
Measured Mass: (M+Na) 802.41531
Error: 4.71 ppm
BnO
NZ
NH
Me
N
O
Me
Me
Me
NHNHBoc
105%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
176
329
245
413
479
629
802
100
200
300
400
500
600
700
800
900
1000
m/z

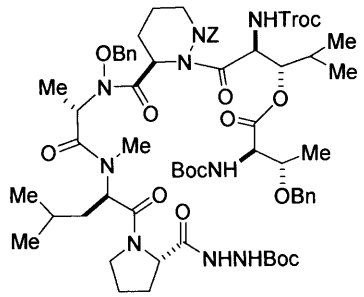

95.0
%T
92.5
90.0
87.5
85.0
82.5
80.0
77.5
75.0
72.5
70.0
67.5
3847.7
3292.3
2929.7
2869.9
1699.2
1645.2
1452.3
1404.1
1367.4
1261.4
1159.1
1016.4
873.7
754.1
700.1
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
NZ
NH
OBn
N
O
Me
N
Me
O
N
O
Me
Me
O
N
NHNHBoc

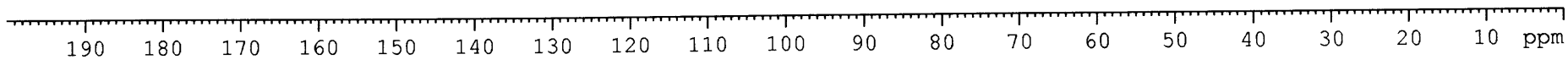


II-AL-105
CDCl3 - 298K

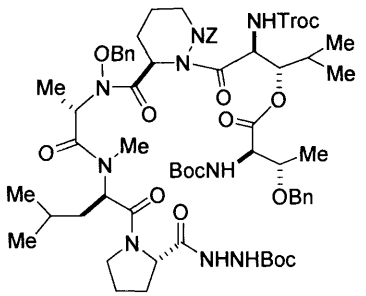


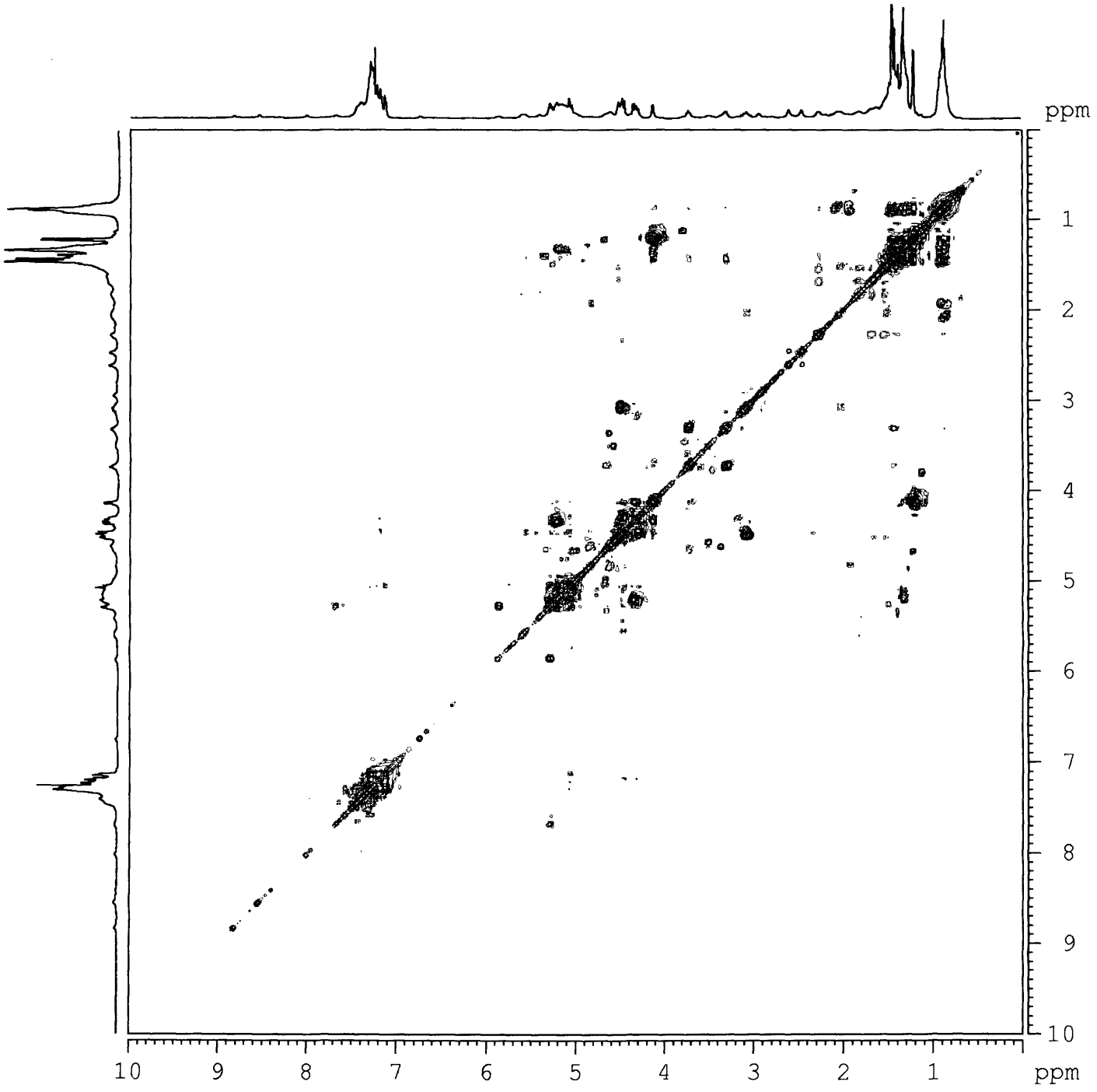
II-AL-105
CDCl3 - 298K



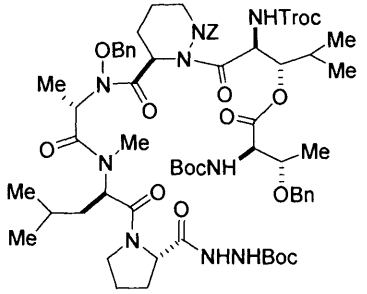


II-AL-105
13C
CDCl3 - 298K

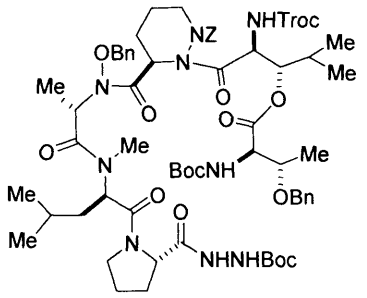


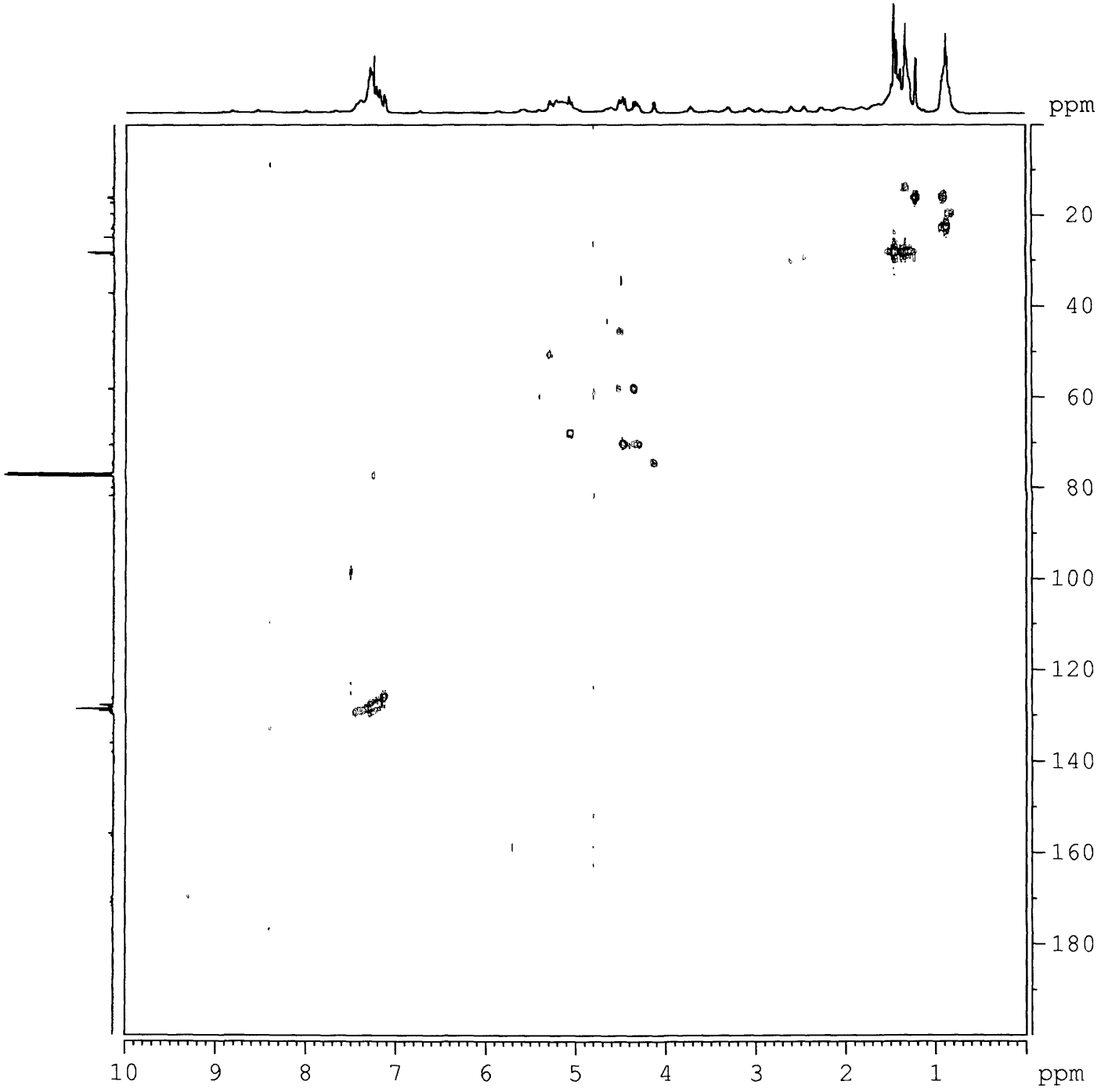


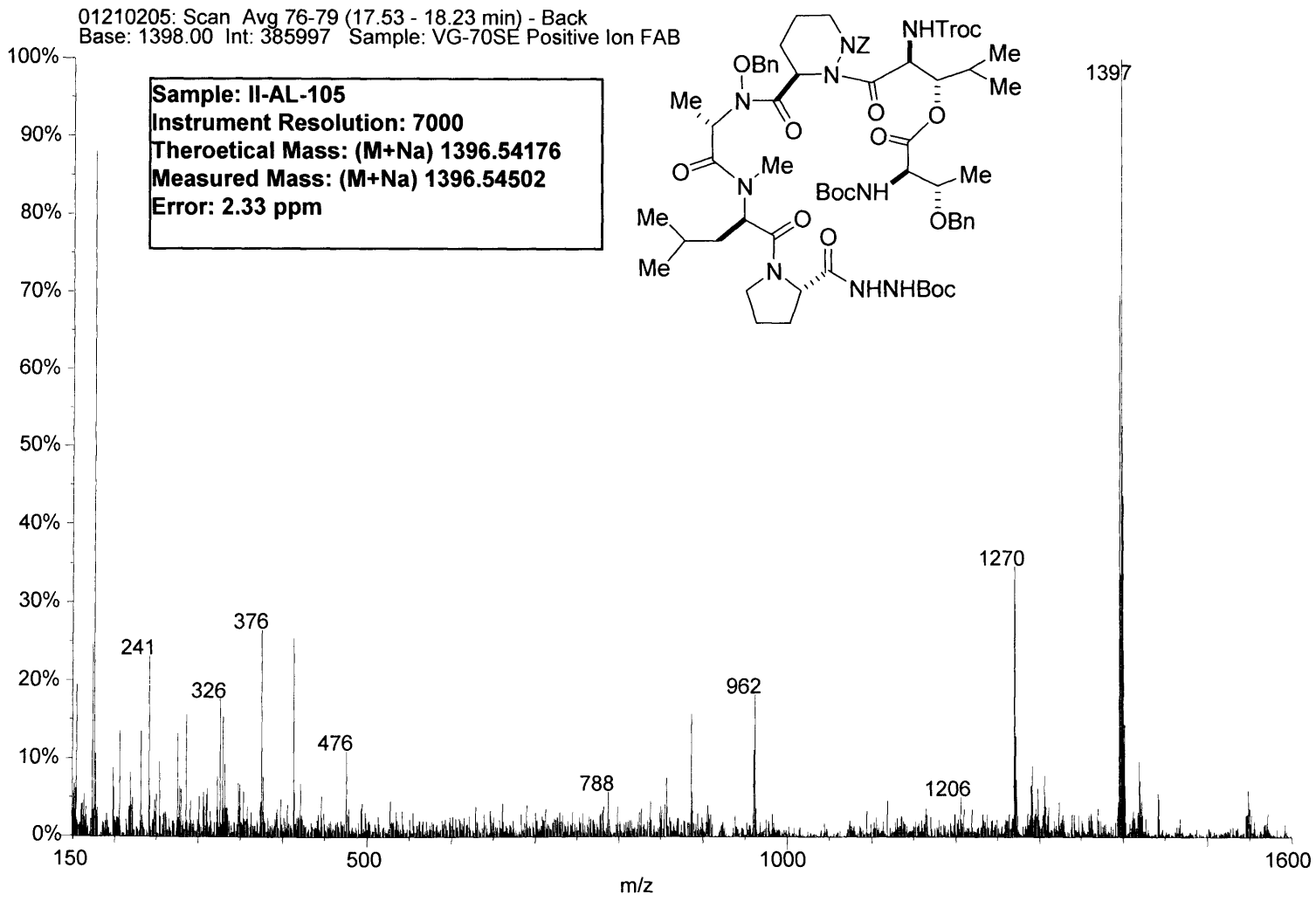
II-AL-105
COSY
CDCl3 - 298K

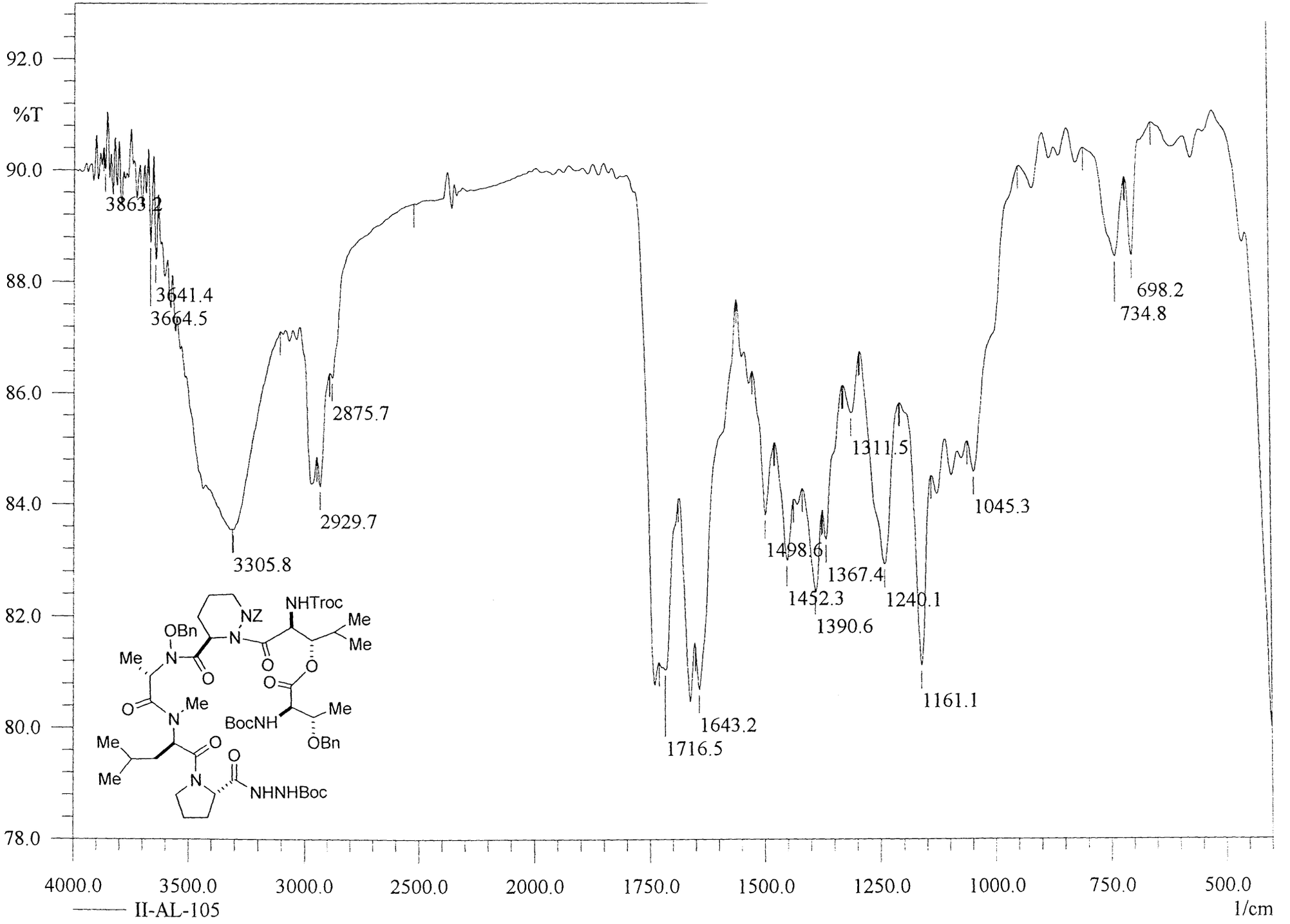


II-AL-105
HMQC
CDCl3 - 298K

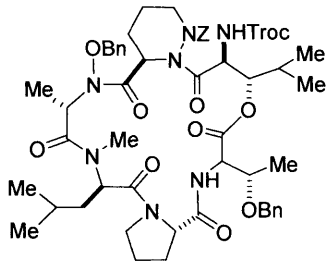




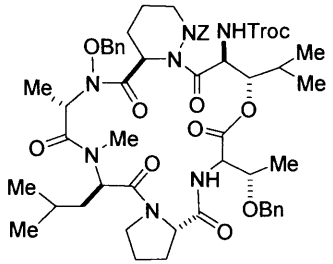

01210205: Scan Avg 76-79 (17.53 - 18.23 min) - Back
Base: 1398.00 Int: 385997 Sample: VG-70SE Positive Ion FAB
Sample: II-AL-105
Instrument Resolution: 7000
Theroetical Mass: (M+Na) 1396.54176
Measured Mass: (M+Na) 1396.54502
Error: 2.33 ppm
NZ
NHTroc
OBn
Me
Me
Me
Me
BocNH
OBn
Me
Me
NHNHBoc
1397
1270
962
376
241
326
476
788
1206
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
150
500
1000
1600
m/z

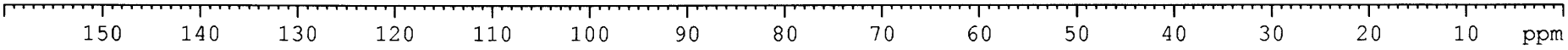

92.0
%T
90.0
88.0
86.0
84.0
82.0
80.0
78.0
3863.2
3641.4
3664.5
2875.7
2929.7
3305.8
1716.5
1643.2
1498.6
1452.3
1390.6
1367.4
1311.5
1240.1
1161.1
1045.3
734.8
698.2
NHTroc
NZ
OBn
Me
Me
Me
Me
Me
BocNH
OBn
Me
Me
NHNHBoc
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
II-AL-105

II-AL-119
CDC13 - 298K

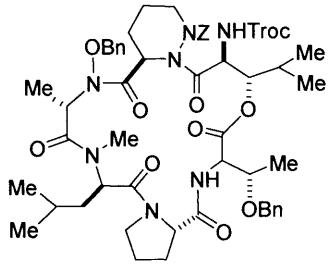


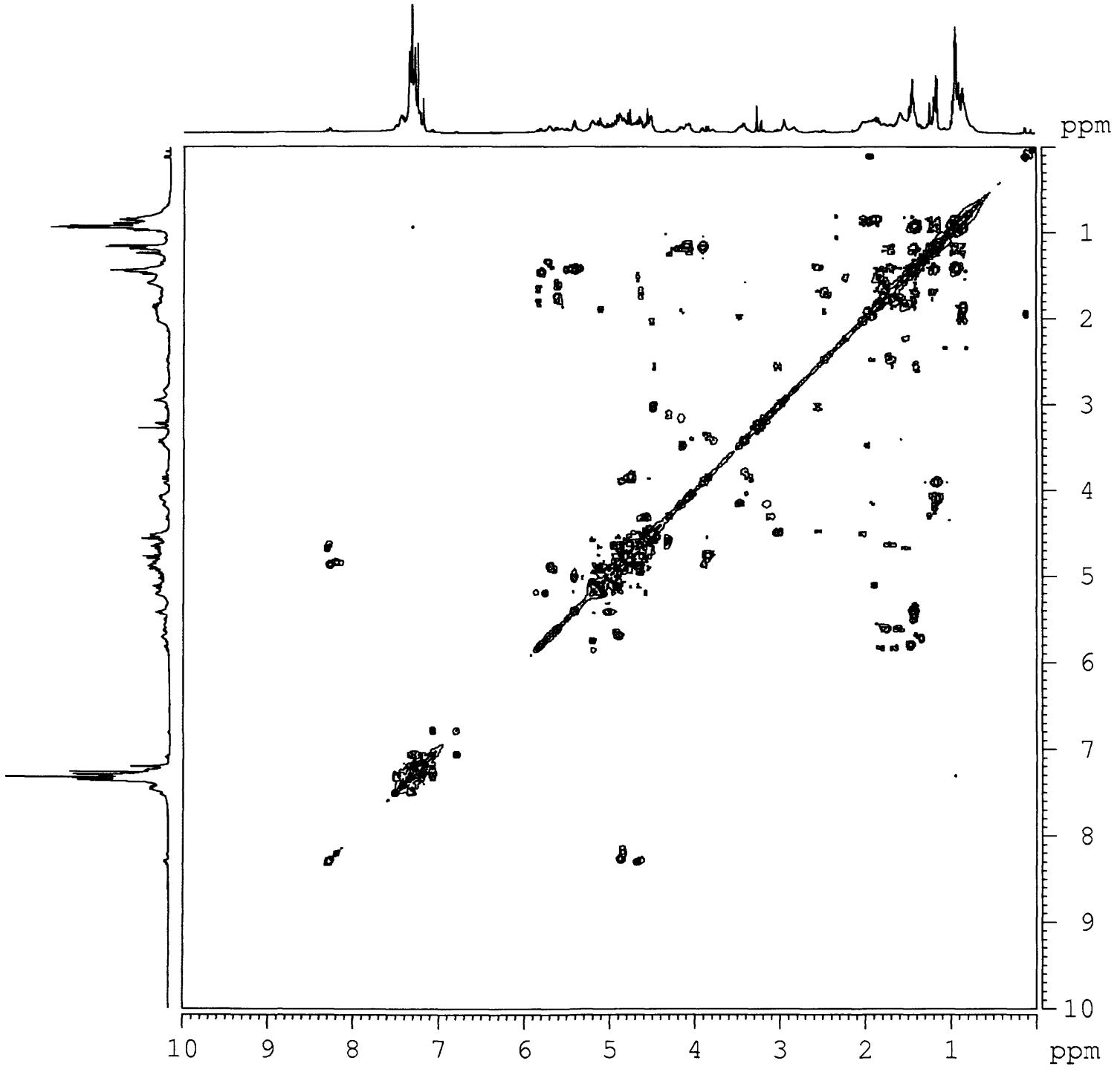
II-AL-119
dept
CDCl3 - 298K



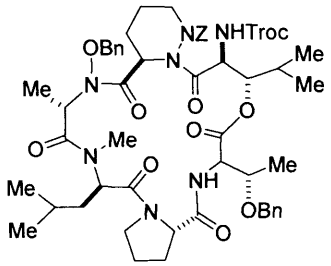


II-AL-119
13C
CDCl3 - 298K

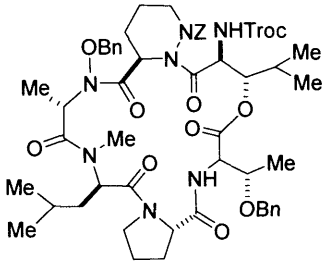


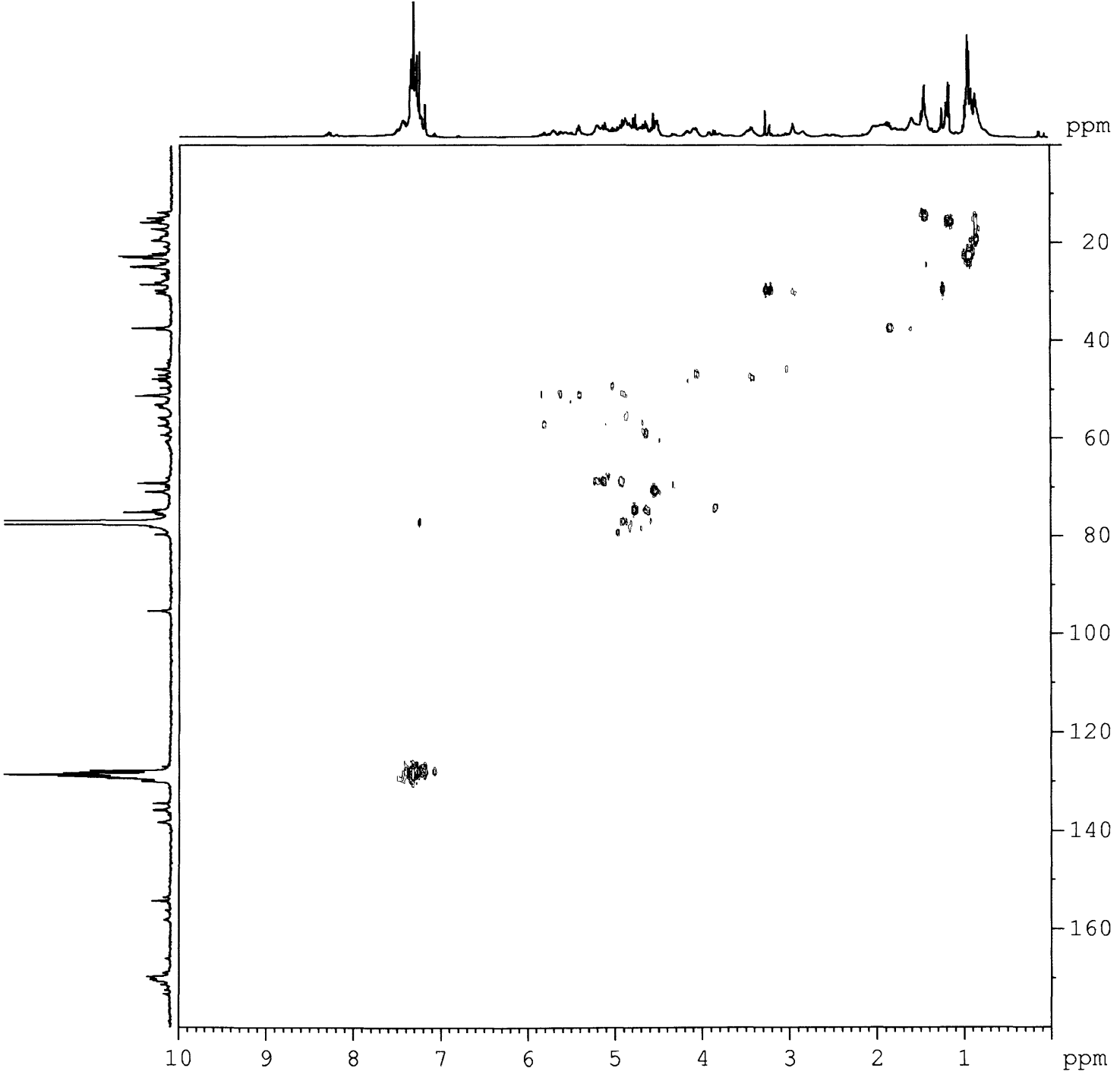


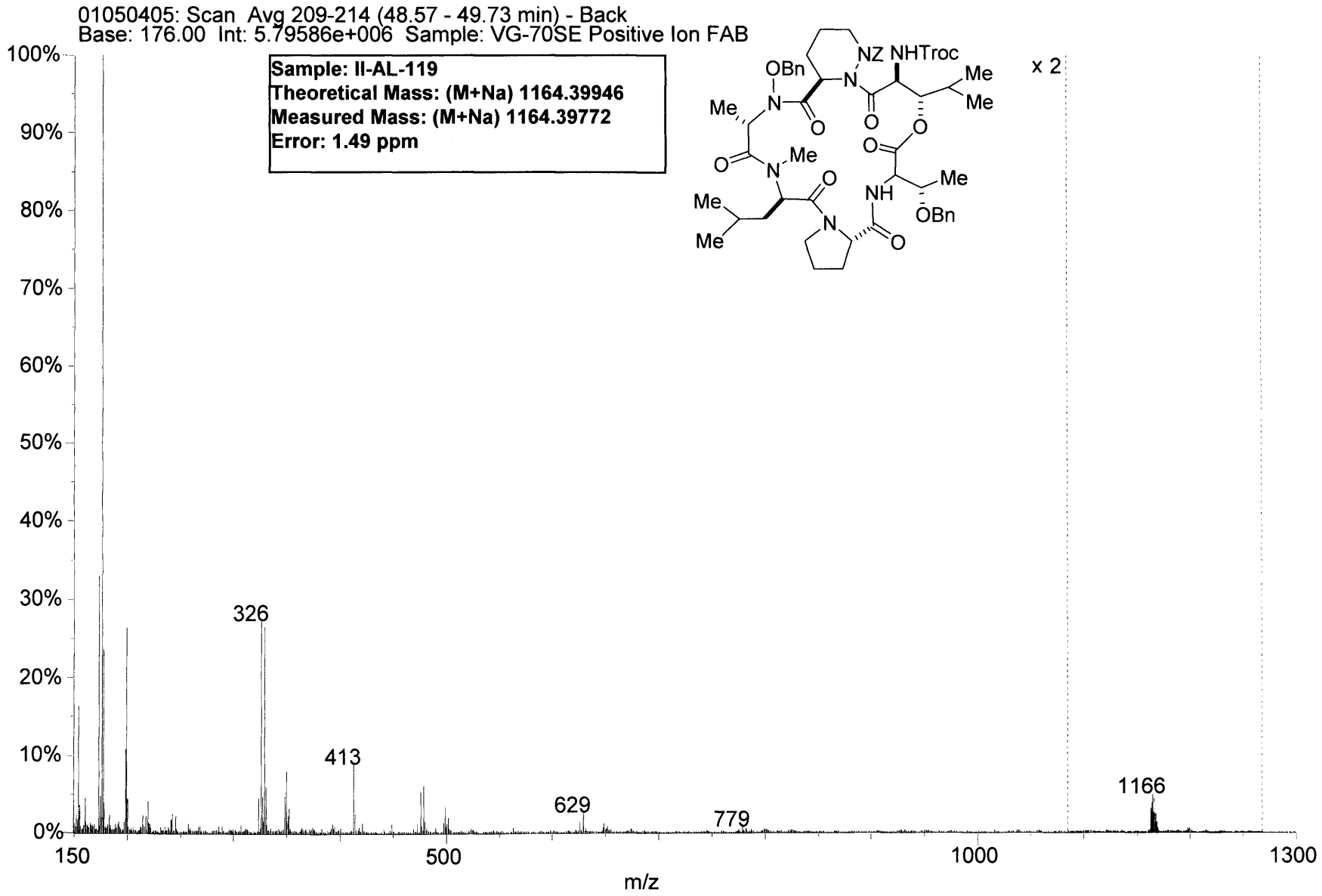
II-AL-119
cosy
CDCl3 - 298K

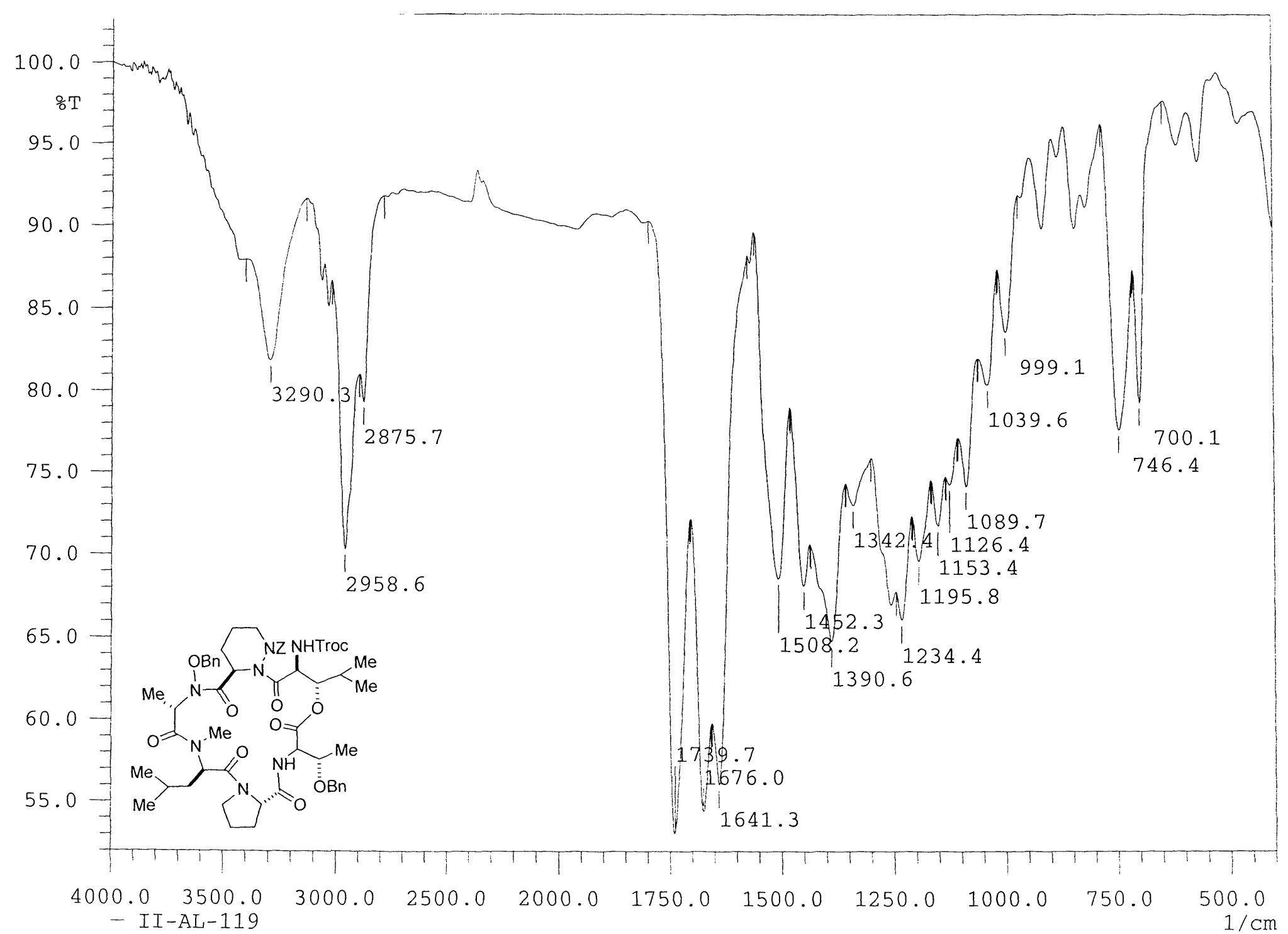


II-AL-119
HMQC
CDCl3 - 298K

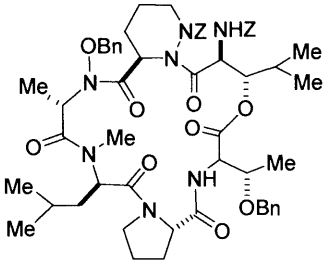




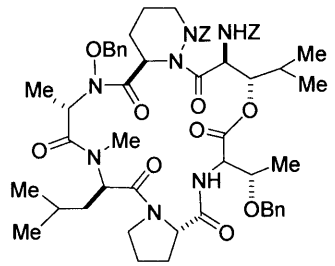

01050405: Scan Avg 209-214 (48.57 - 49.73 min) - Back
Base: 176.00 Int: 5.79586e+006 Sample: VG-70SE Positive Ion FAB
Sample: II-AL-119
Theoretical Mass: (M+Na) 1164.39946
Measured Mass: (M+Na) 1164.39772
Error: 1.49 ppm
x 2
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
326
413
629
779
1166
150
500
1000
1300
m/z


100.0
%T
95.0
90.0
85.0
80.0
75.0
70.0
65.0
60.0
55.0
3290.3
2875.7
2958.6
1739.7
1676.0
1641.3
1508.2
1452.3
1390.6
1342.4
1234.4
1195.8
1153.4
1126.4
1089.7
1039.6
999.1
746.4
700.1
NZ NHTroc
OBn
Me
Me
Me
Me
Me
Me
Me
NH
OBn
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
II-AL-119

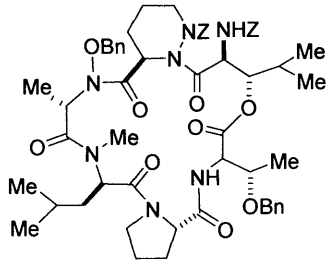
II-AL-114
CDCl3 - 298K

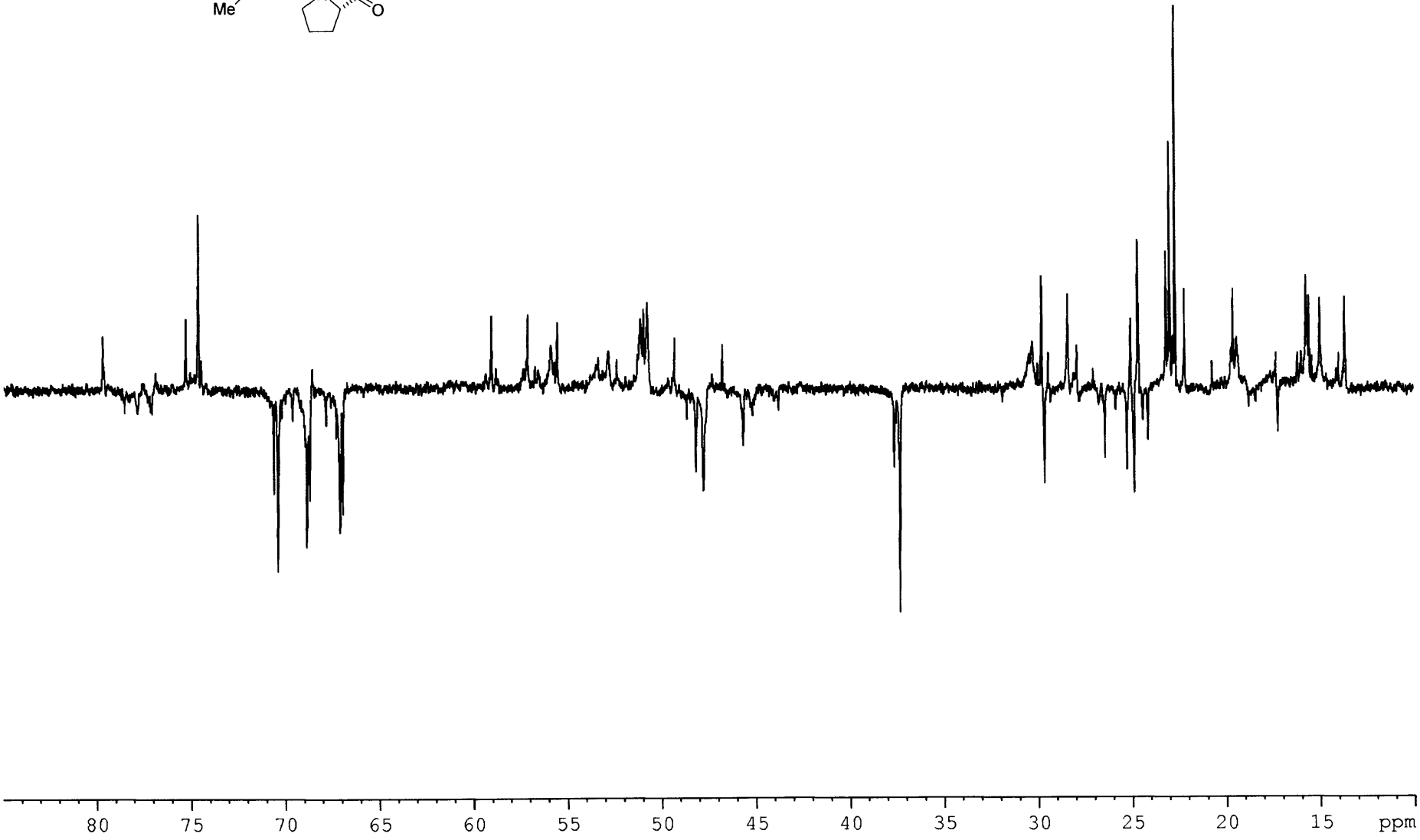


II-AL-114
DEPT
CDCl3 - 298K

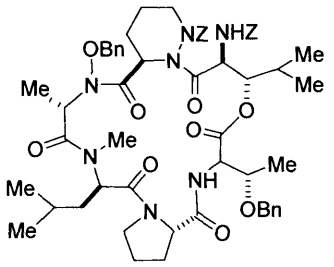


II-AL-114
DEPT
CDC13 - 298K

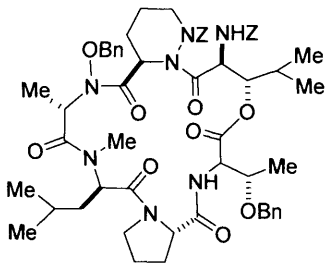


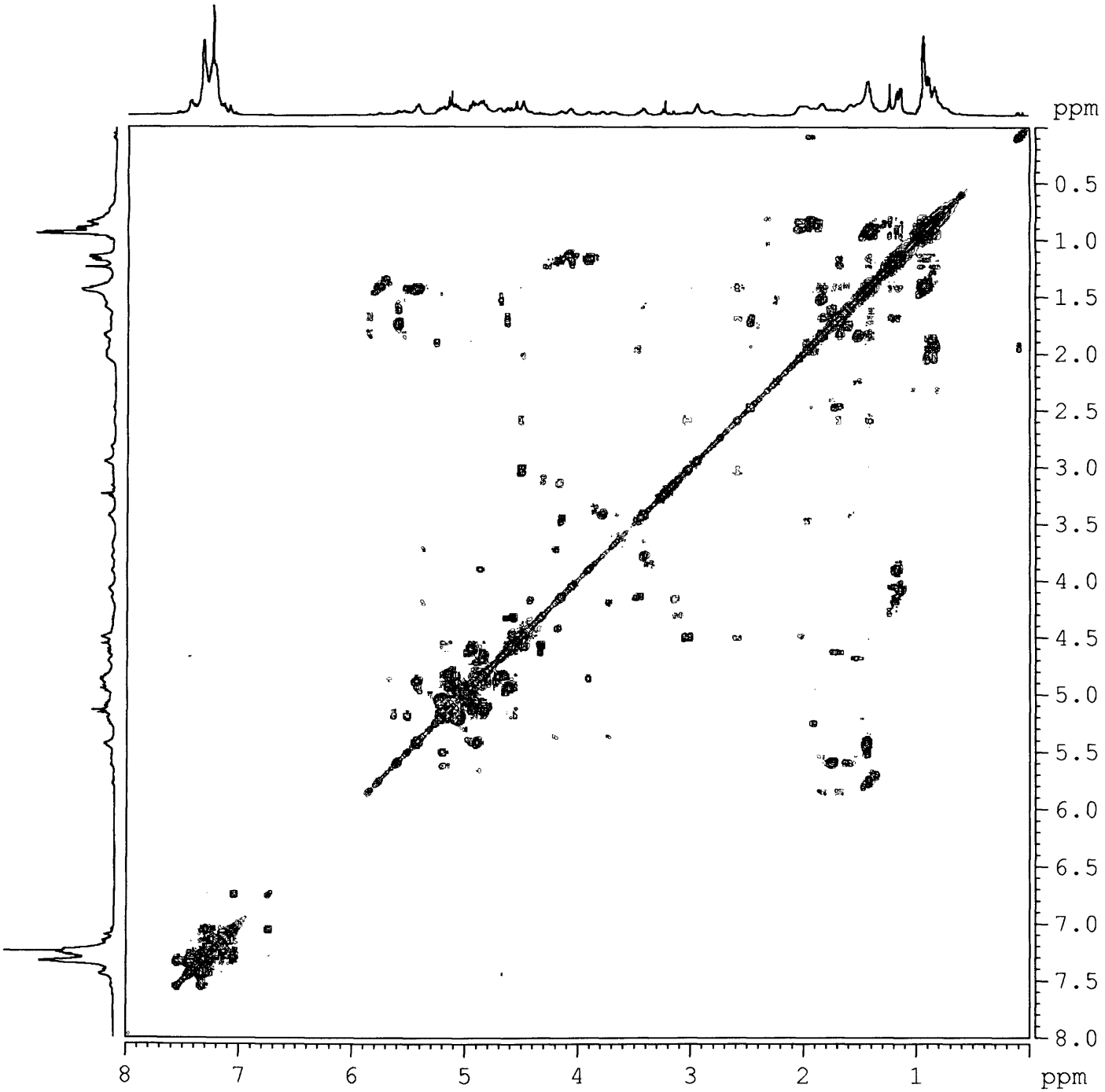


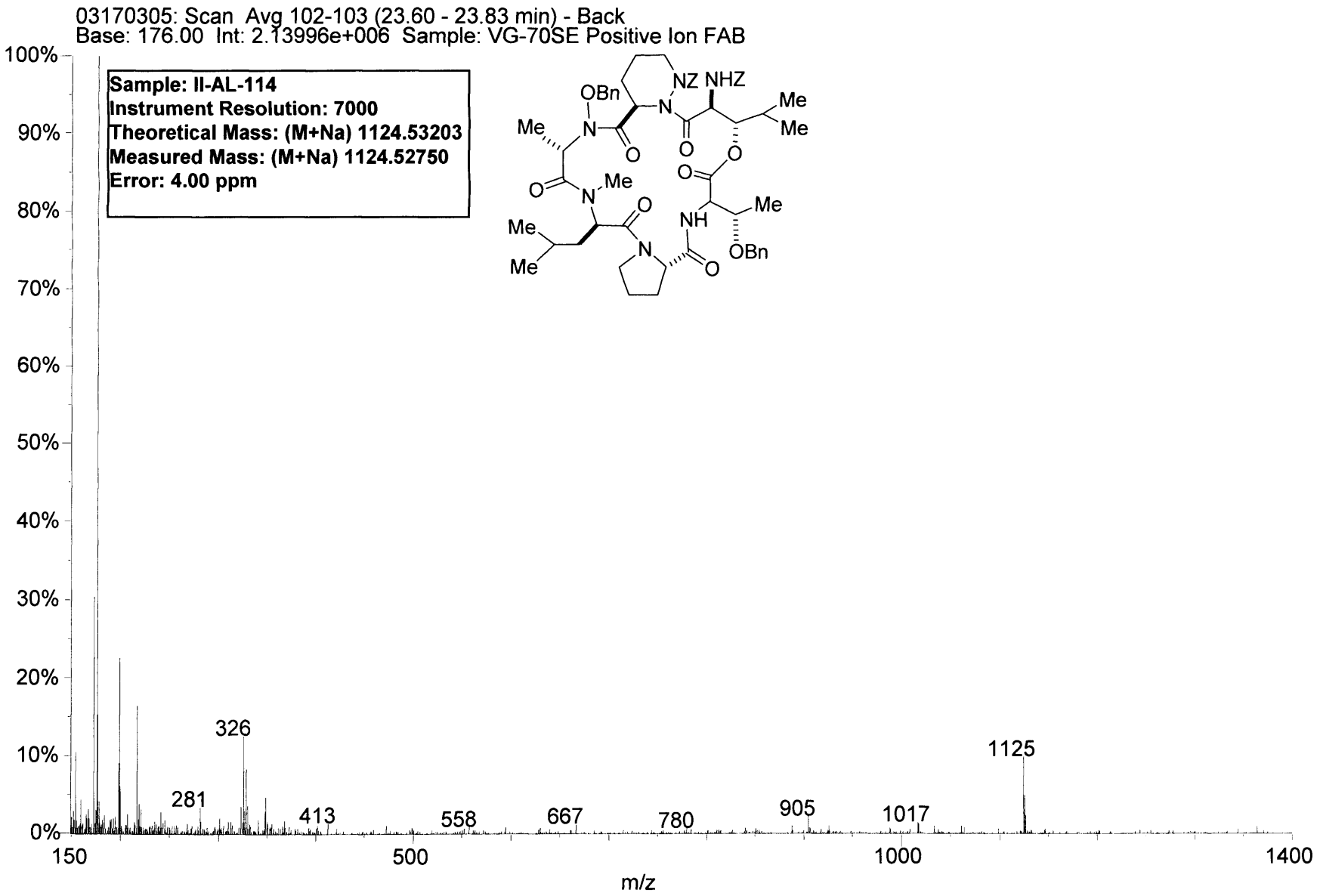
II-AL-114
13C
CDCl3 - 298K

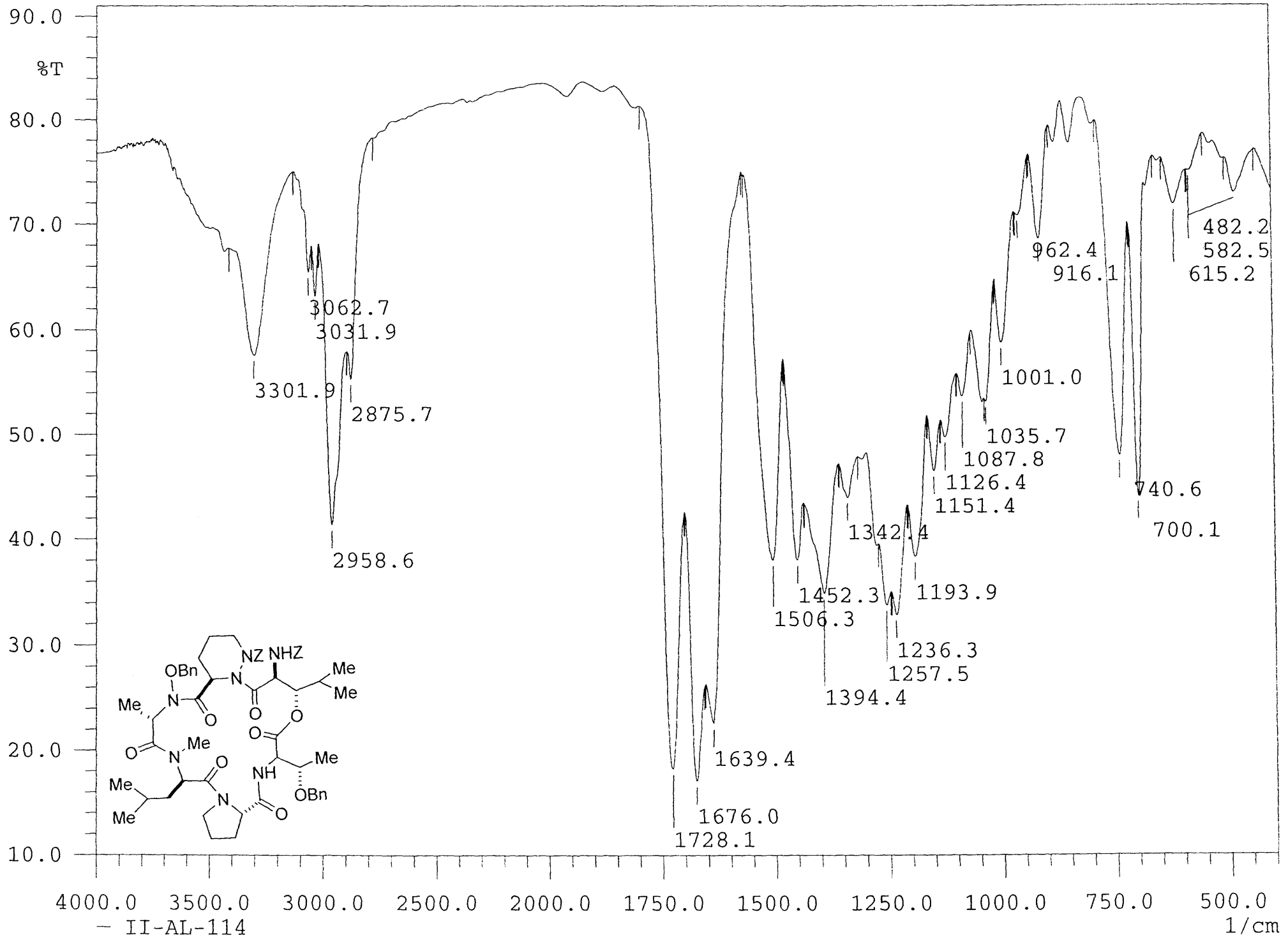


II-AL-114
COSY
CDCl3 - 298K

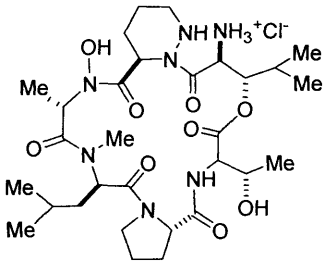




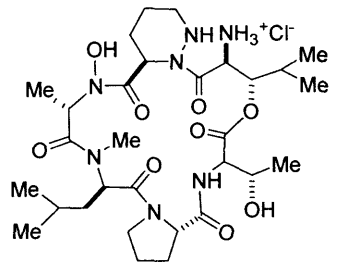

03170305: Scan Avg 102-103 (23.60 - 23.83 min) - Back
Base: 176.00 Int: 2.13996e+006 Sample: VG-70SE Positive Ion FAB
Sample: II-AL-114
Instrument Resolution: 7000
Theoretical Mass: (M+Na) 1124.53203
Measured Mass: (M+Na) 1124.52750
Error: 4.00 ppm
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
326
281
413
558
667
780
905
1017
1125
150
500
1000
1400
m/z


90.0
%T
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
3062.7
3031.9
3301.9
2875.7
2958.6
1728.1
1676.0
1639.4
1506.3
1452.3
1394.4
1342.4
1257.5
1236.3
1193.9
1151.4
1126.4
1087.8
1035.7
1001.0
962.4
916.1
740.6
700.1
615.2
582.5
482.2
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
— II-AL-114
NZ NHZ
OBn
Me
Me
Me
Me
Me
Me
Me
NH
OBn
Me
Me

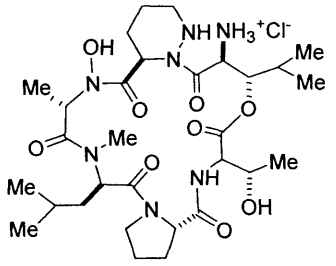
II-AL-124
MeOD - 298K

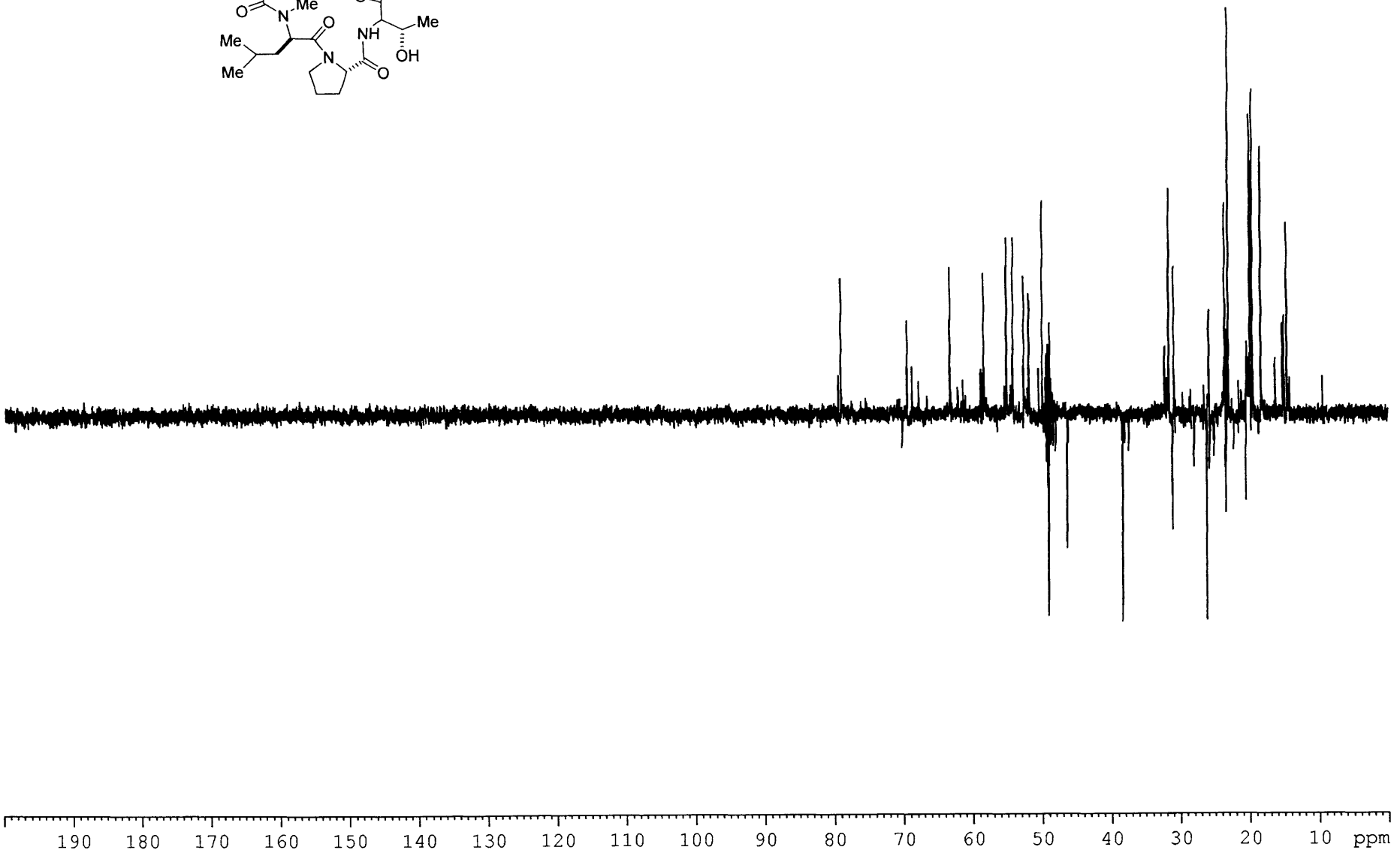


II-AL-124
MeOD - 298K

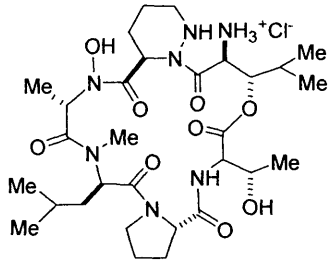


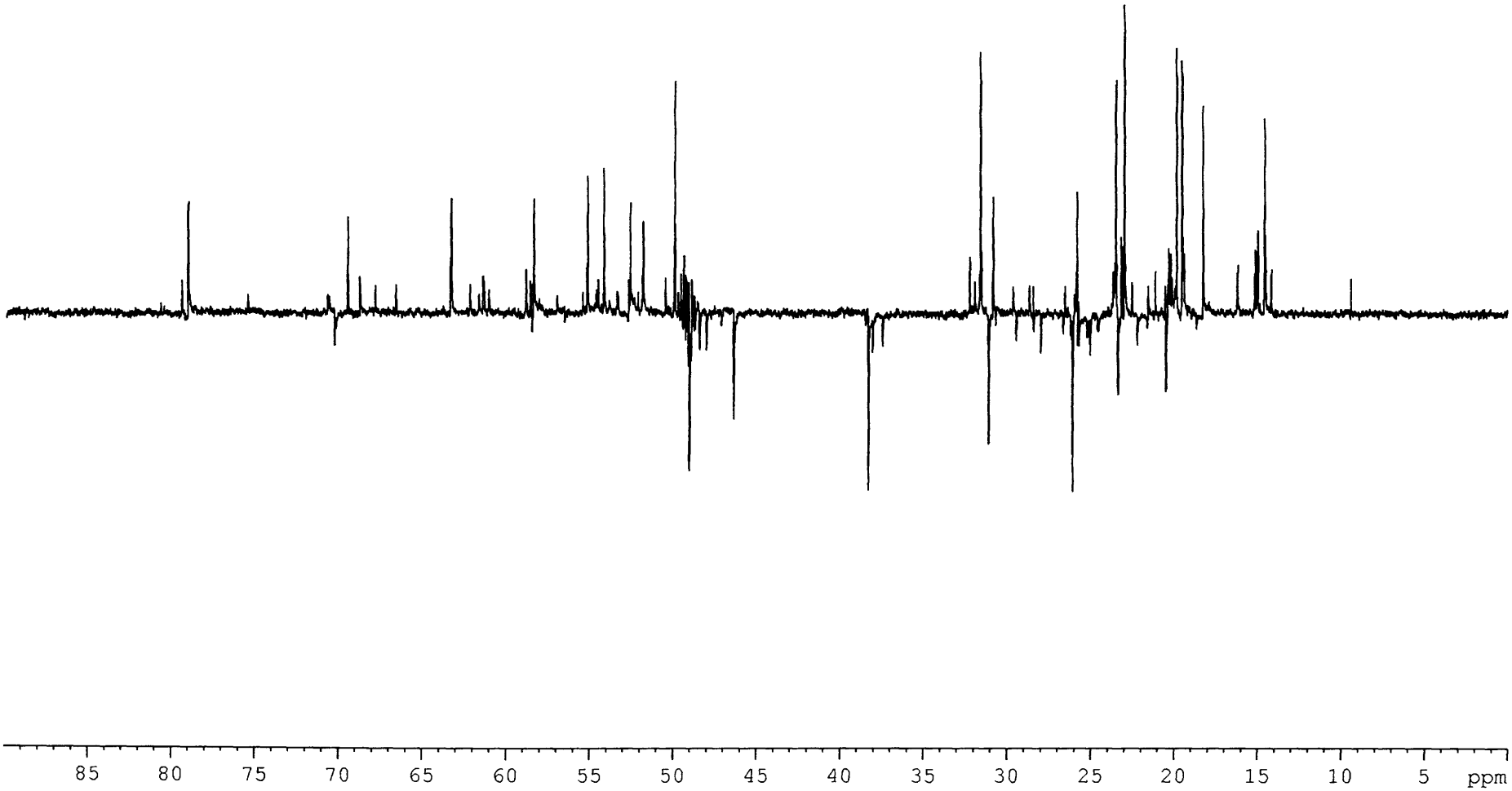
II-AL-124
DEPT
MeOD - 298K



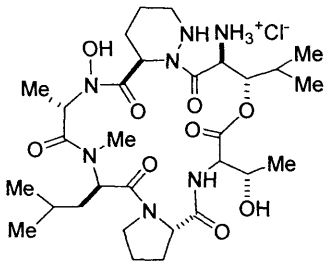


II-AL-124
DEPT
MeOD - 298K

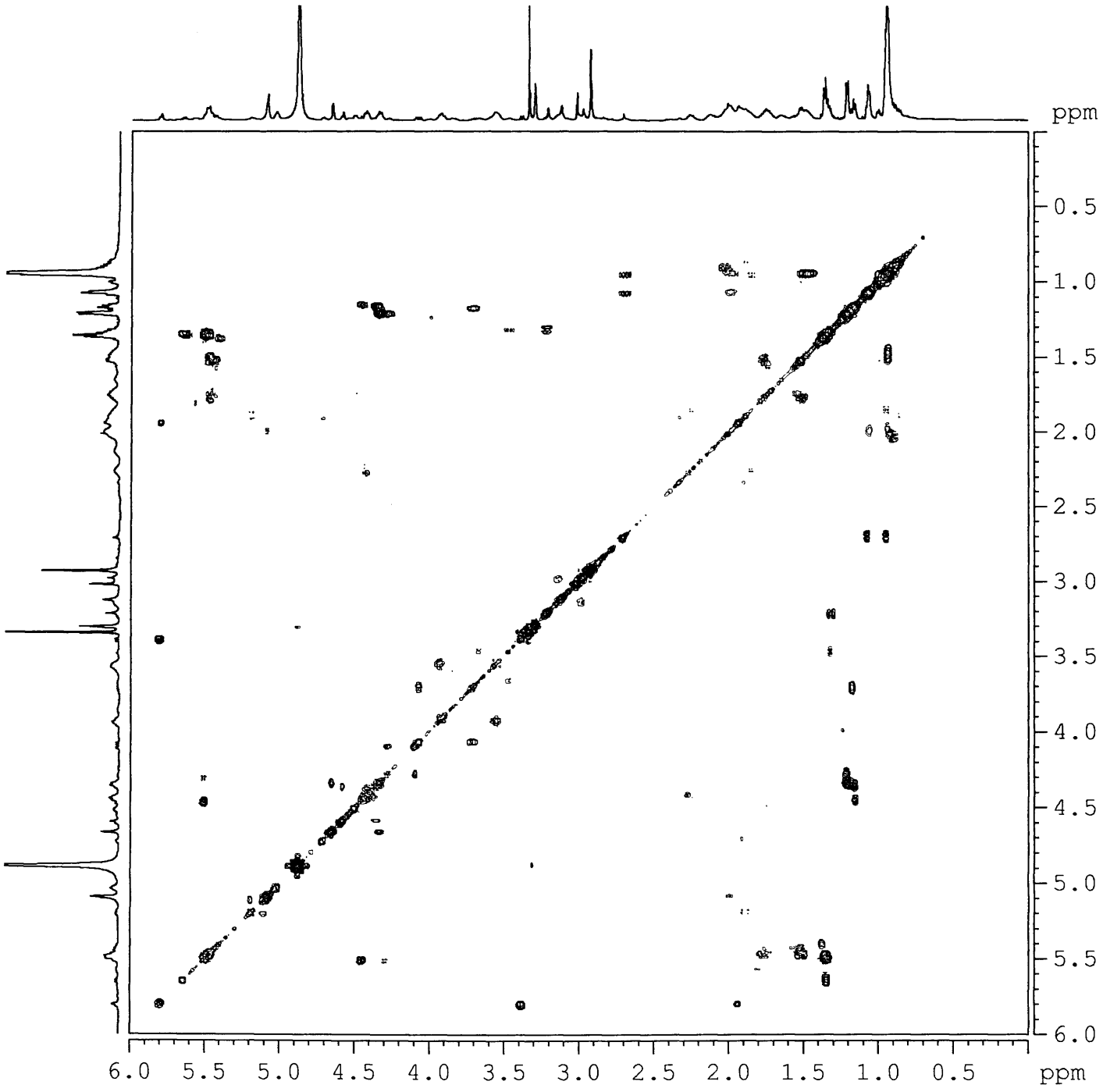


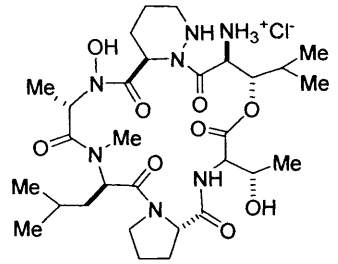


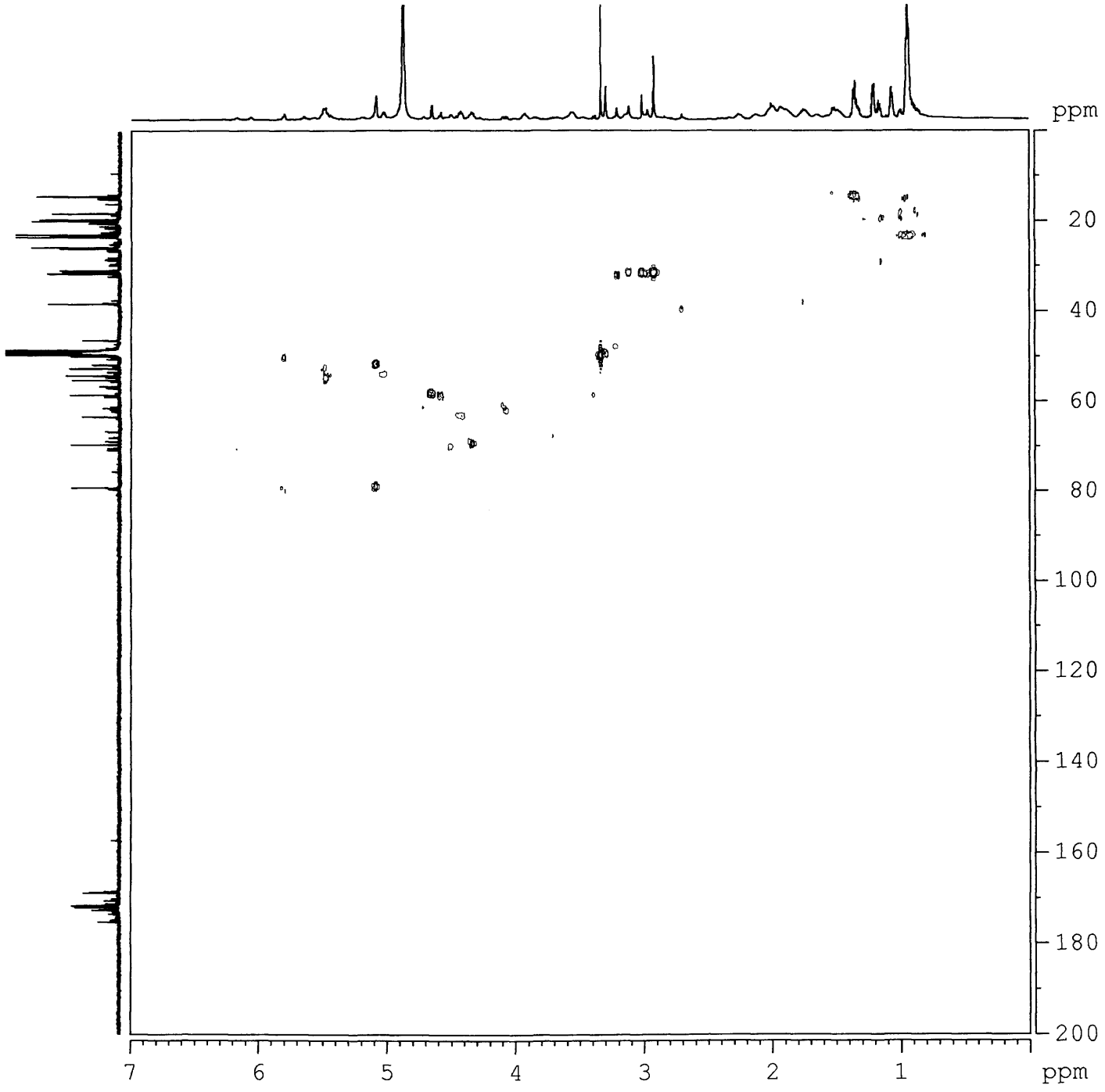
II-AL-124
13C
MeOD - 298K



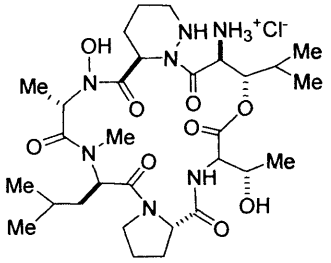
II-AL-124
cosy
MeOD - 298K

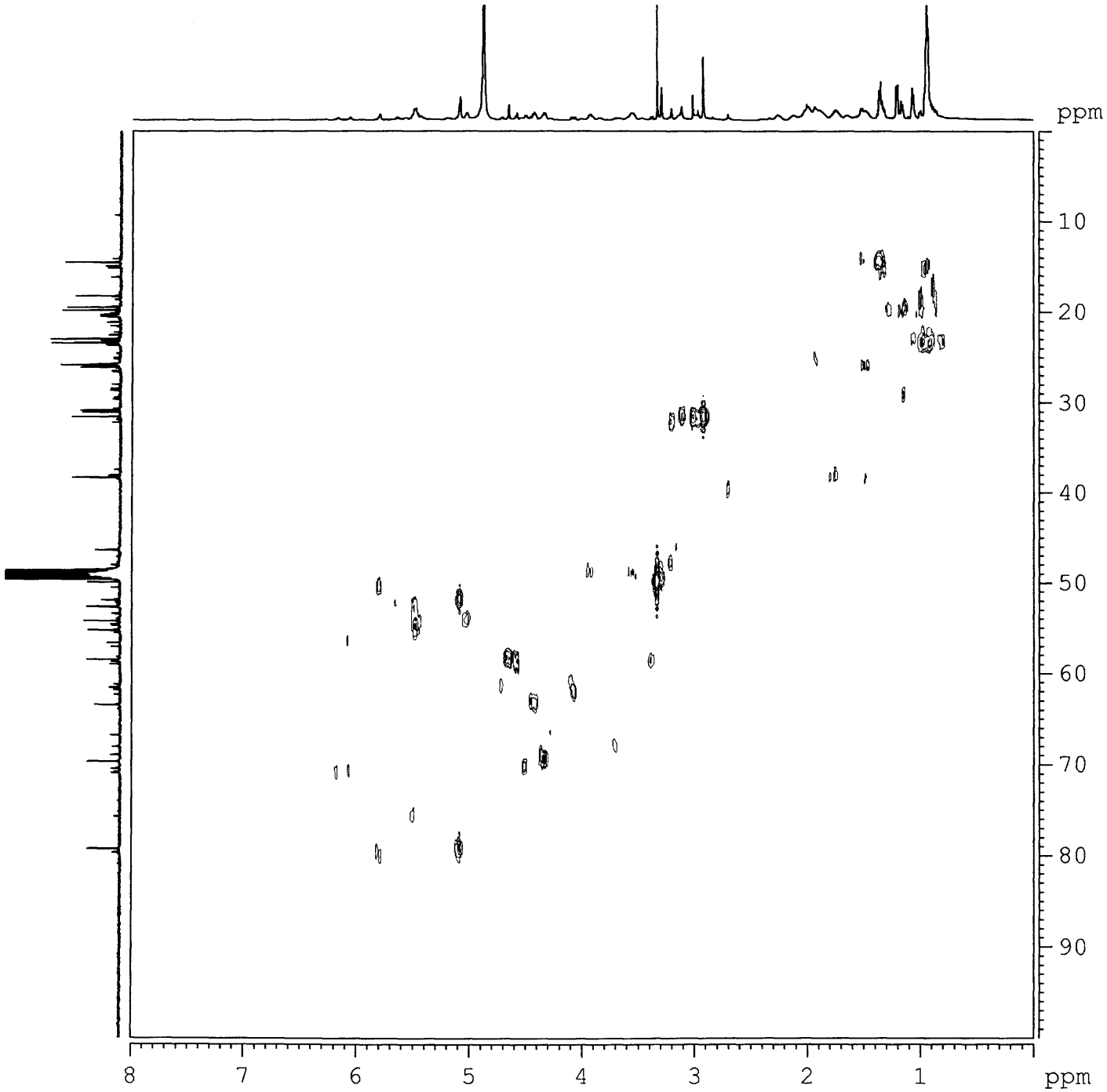




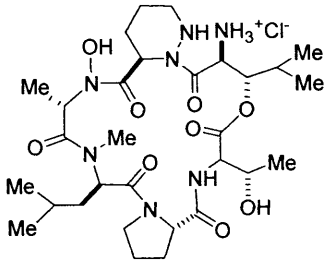


II-AL-124
HMQC
MeOD - 298K

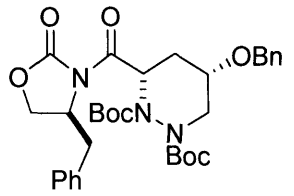




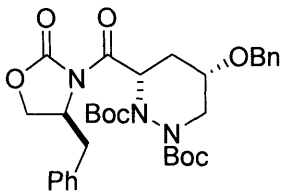
II-AL-124
HMQC
MeOD - 298K

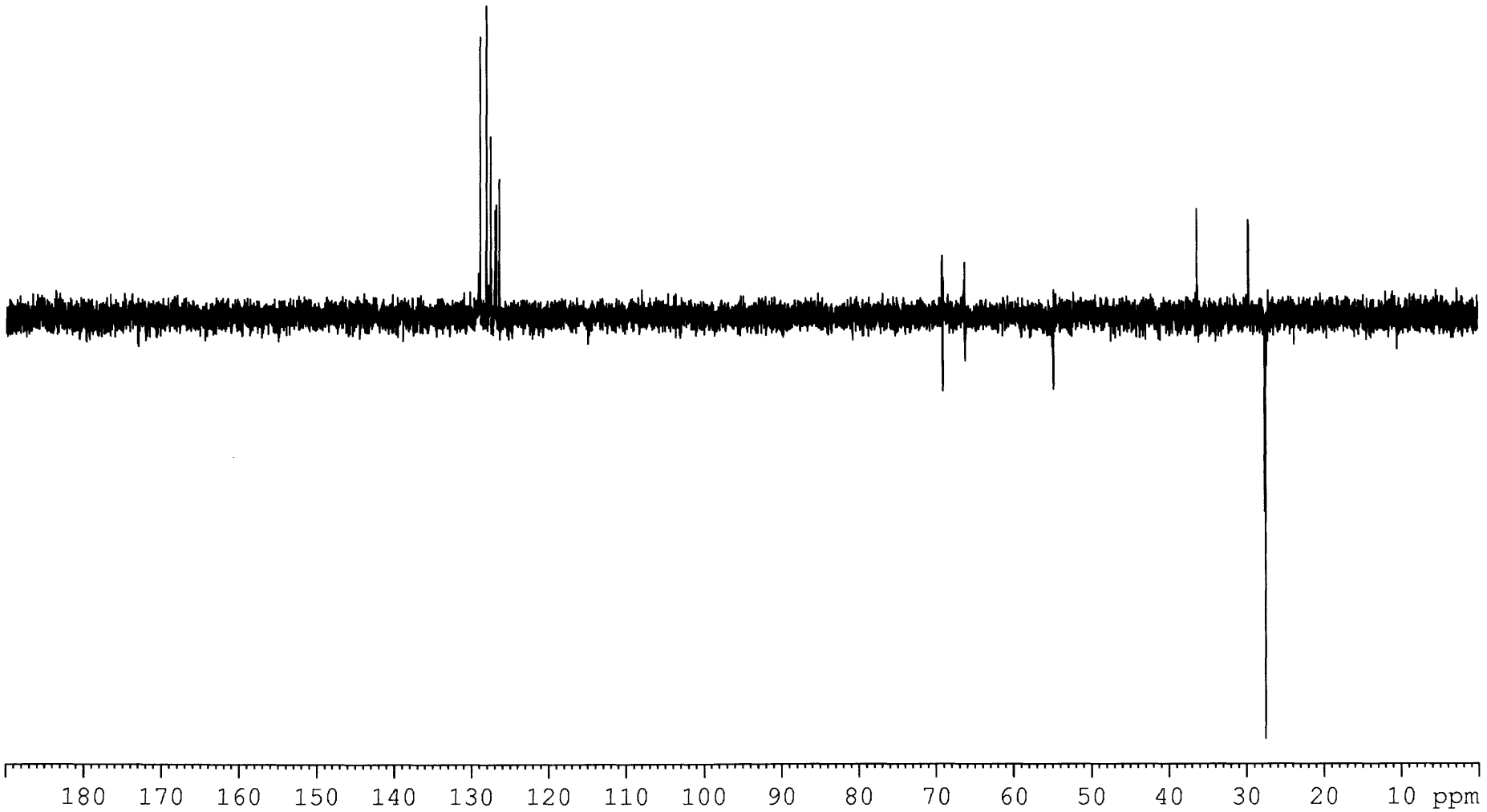


I-AL-127
DMSO - 353K

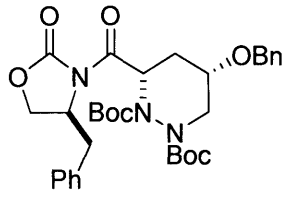


I-AL-127
DEPT
DMSO - 333K

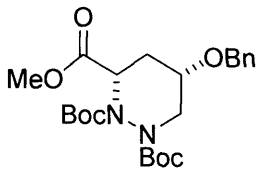




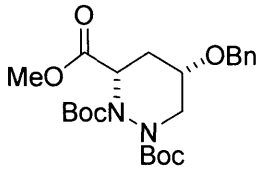
I-AL-127
13C
DMSO - 353K



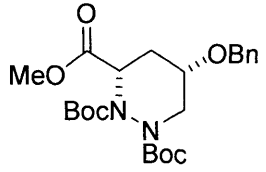
I-AL-129
DMSO - 353k

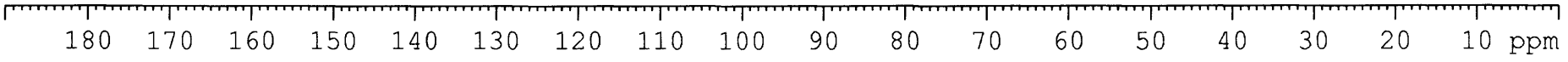


I-AL-129
DMSO - 373K

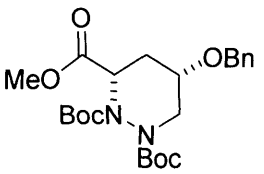


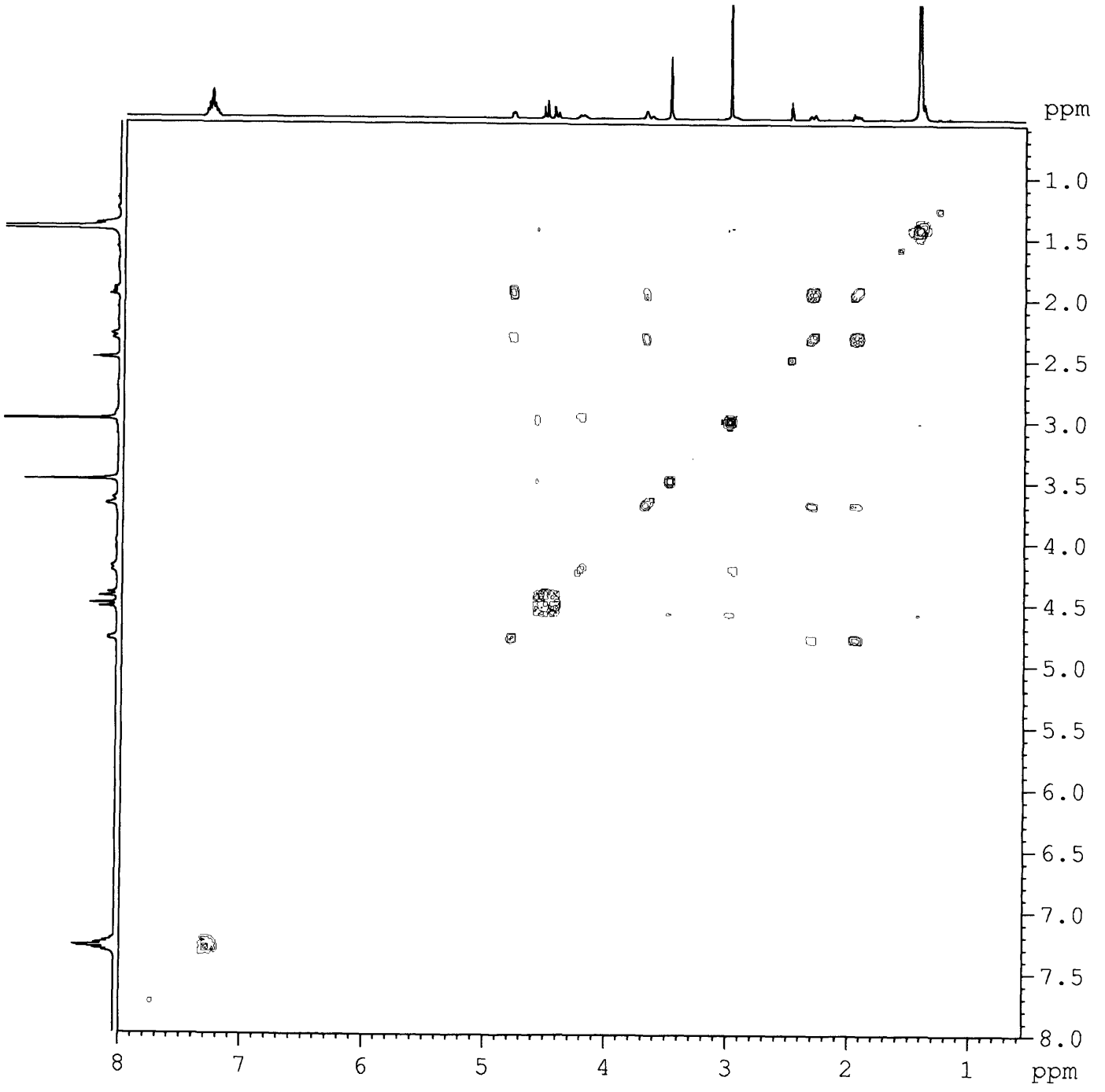
I-AL-129
DEPT
DMSO - 353K



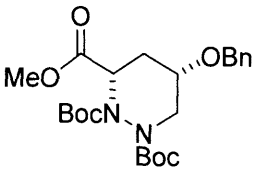


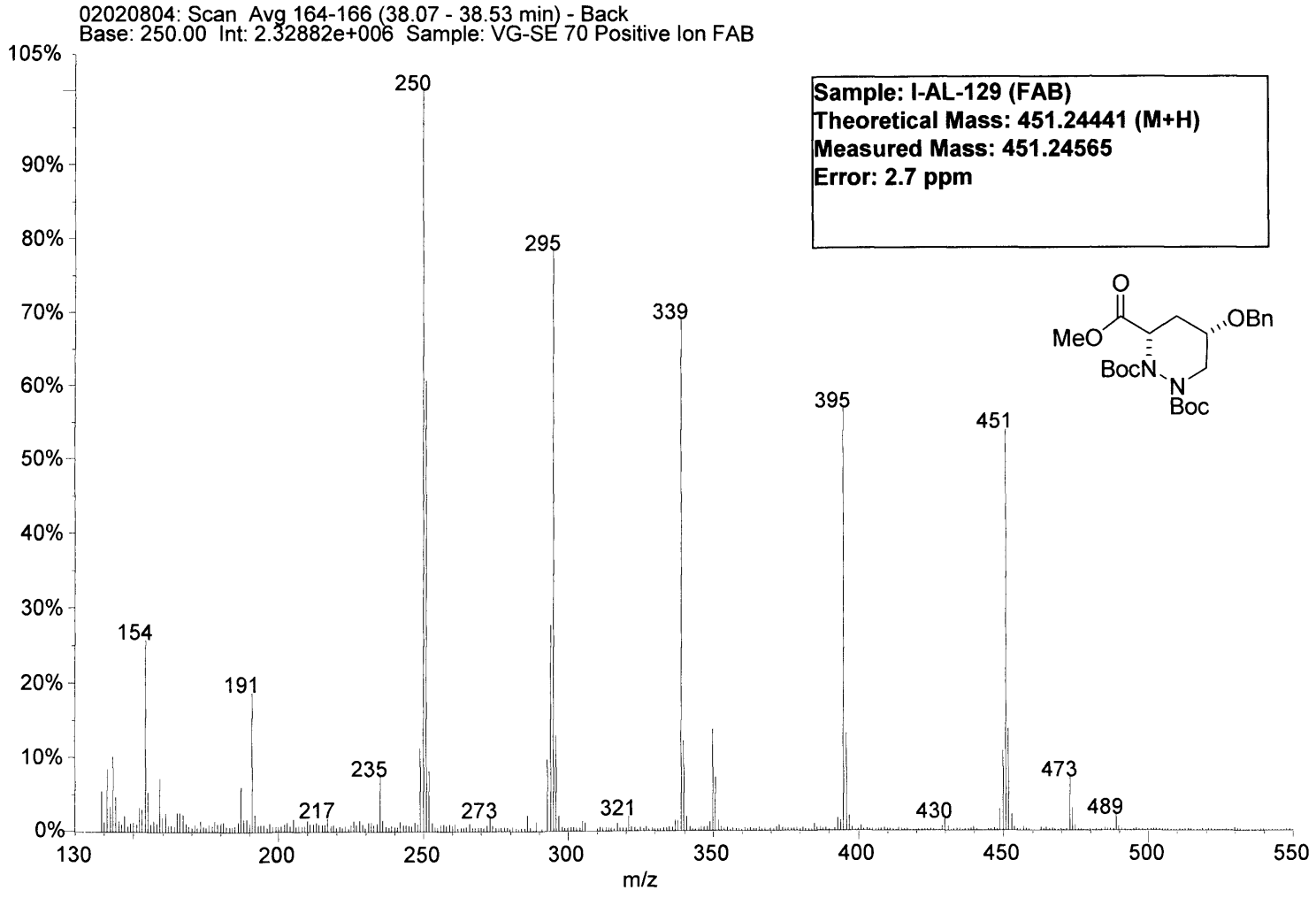
I-AL-129
13C
DMSO - 353K



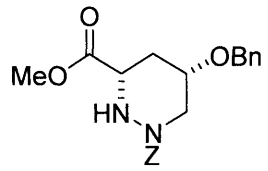


I-AL-129
COSY
CDCl3 - 353K

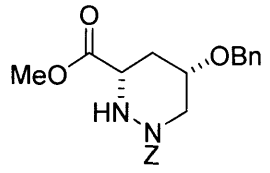


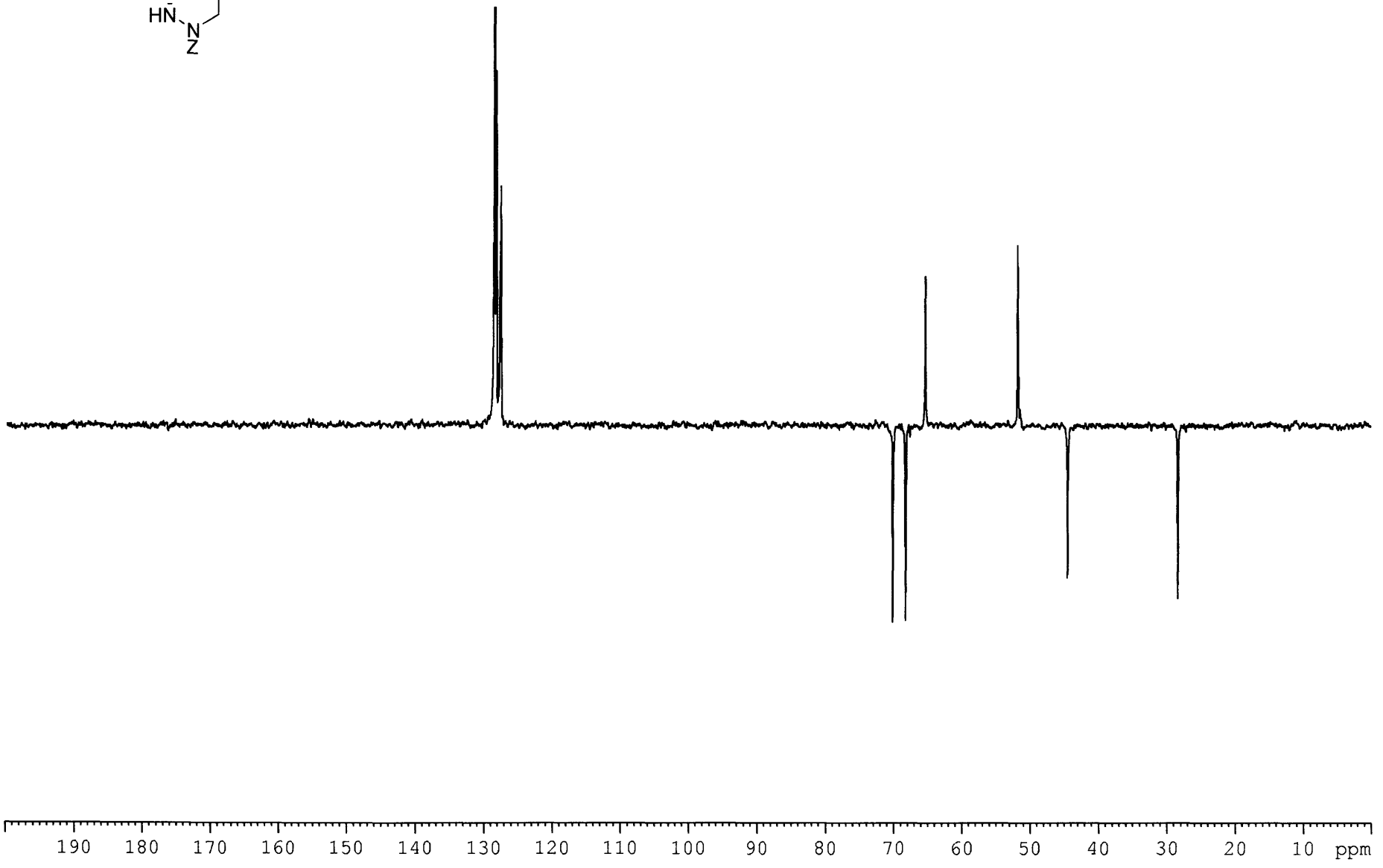

02020804: Scan Avg 164-166 (38.07 - 38.53 min) - Back
Base: 250.00 Int: 2.32882e+006 Sample: VG-SE 70 Positive Ion FAB
Sample: I-AL-129 (FAB)
Theoretical Mass: 451.24441 (M+H)
Measured Mass: 451.24565
Error: 2.7 ppm
MeO
BocN
N
Boc
OBn
O
105%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
130
200
250
300
350
400
450
500
550
m/z
250
295
339
395
451
154
191
217
235
273
321
430
473
489

I-AL-162-1
C6D6 - 298K

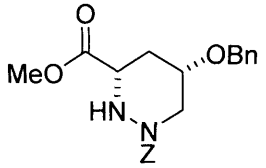


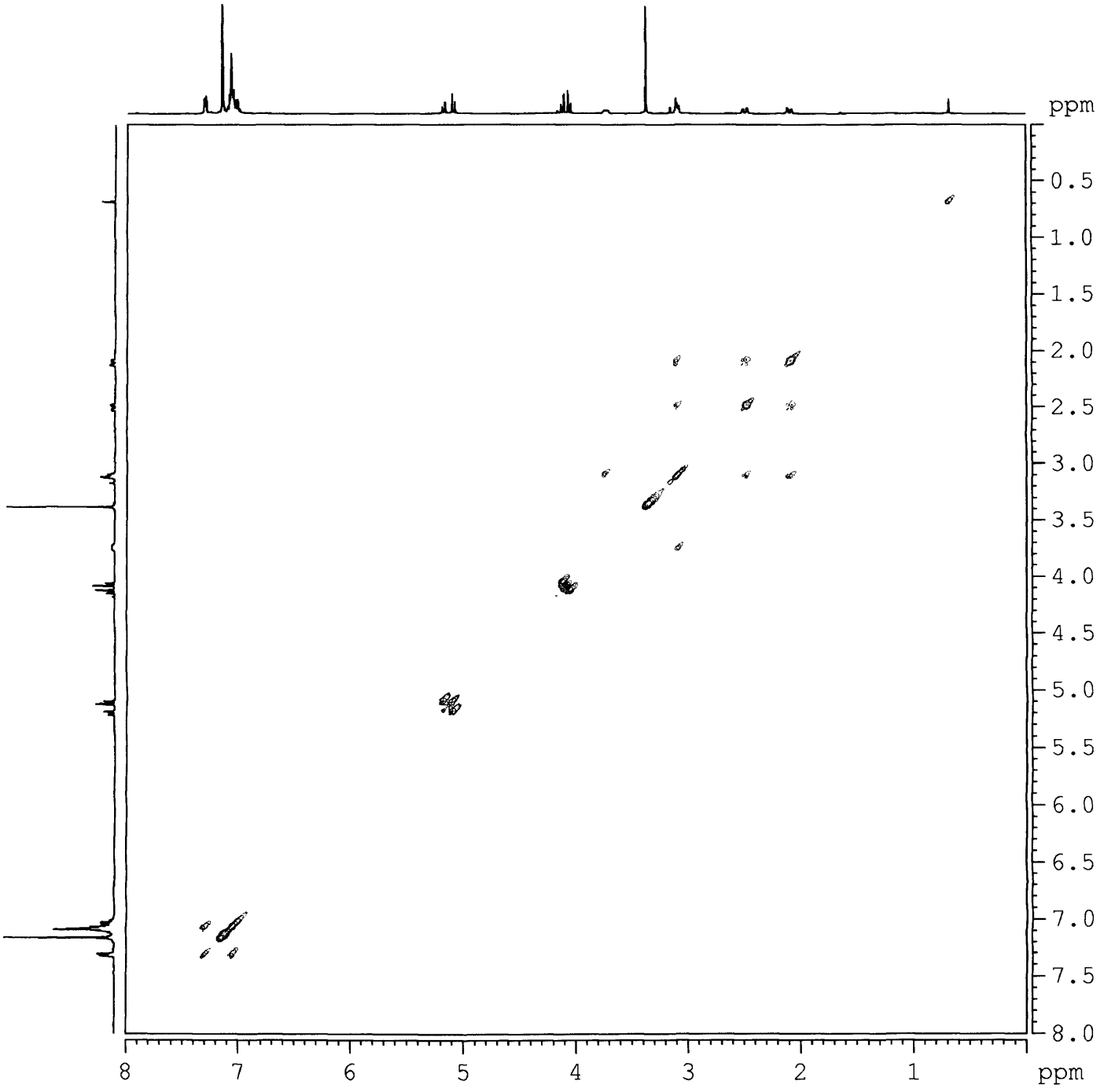
I-AL-162-1
dept
C6D6 - 298K



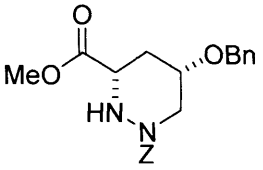


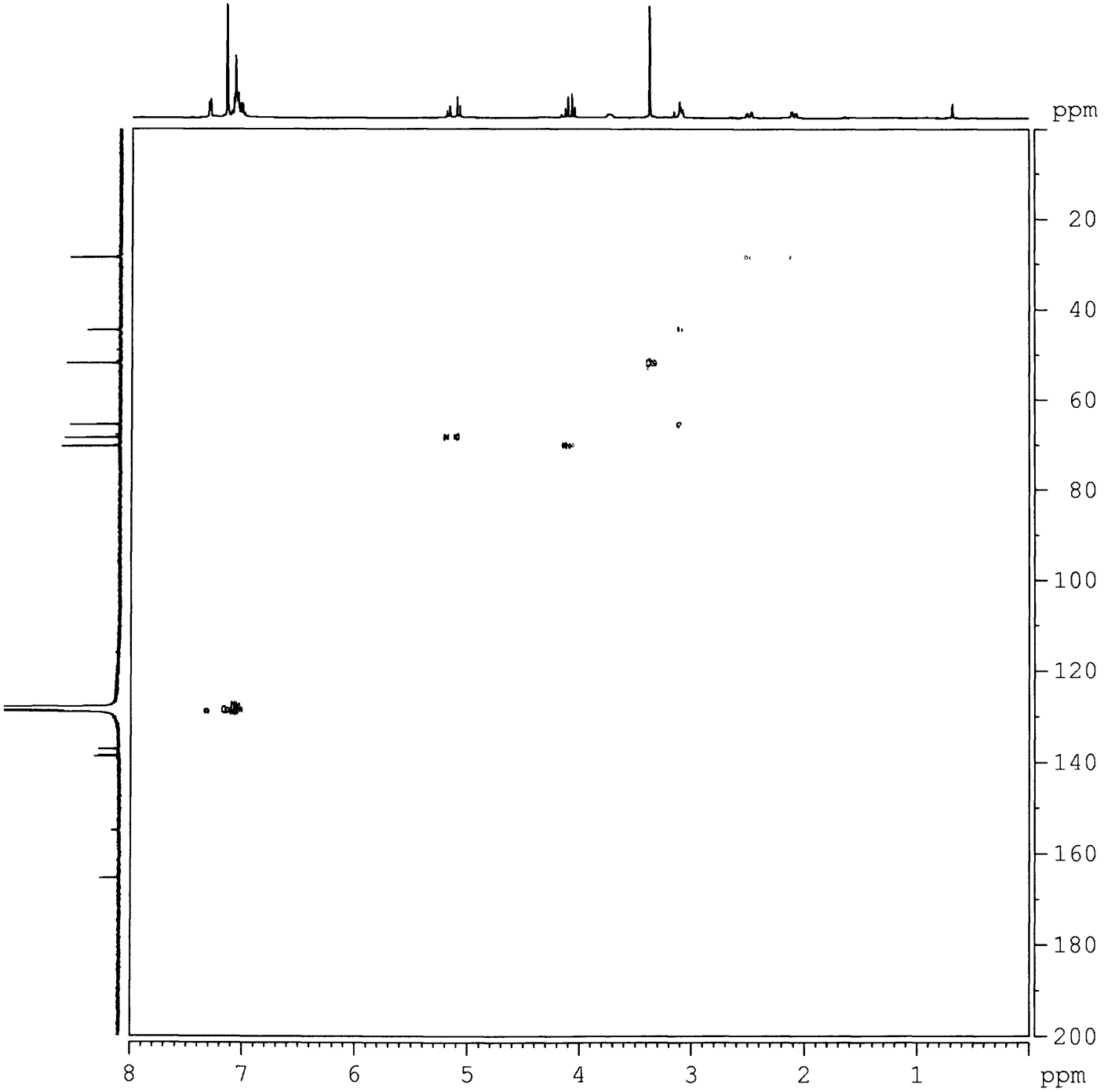
I-AL-162-1
13 C
C6D6 - 298K



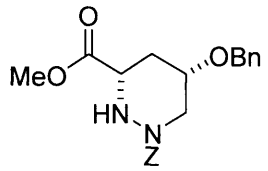


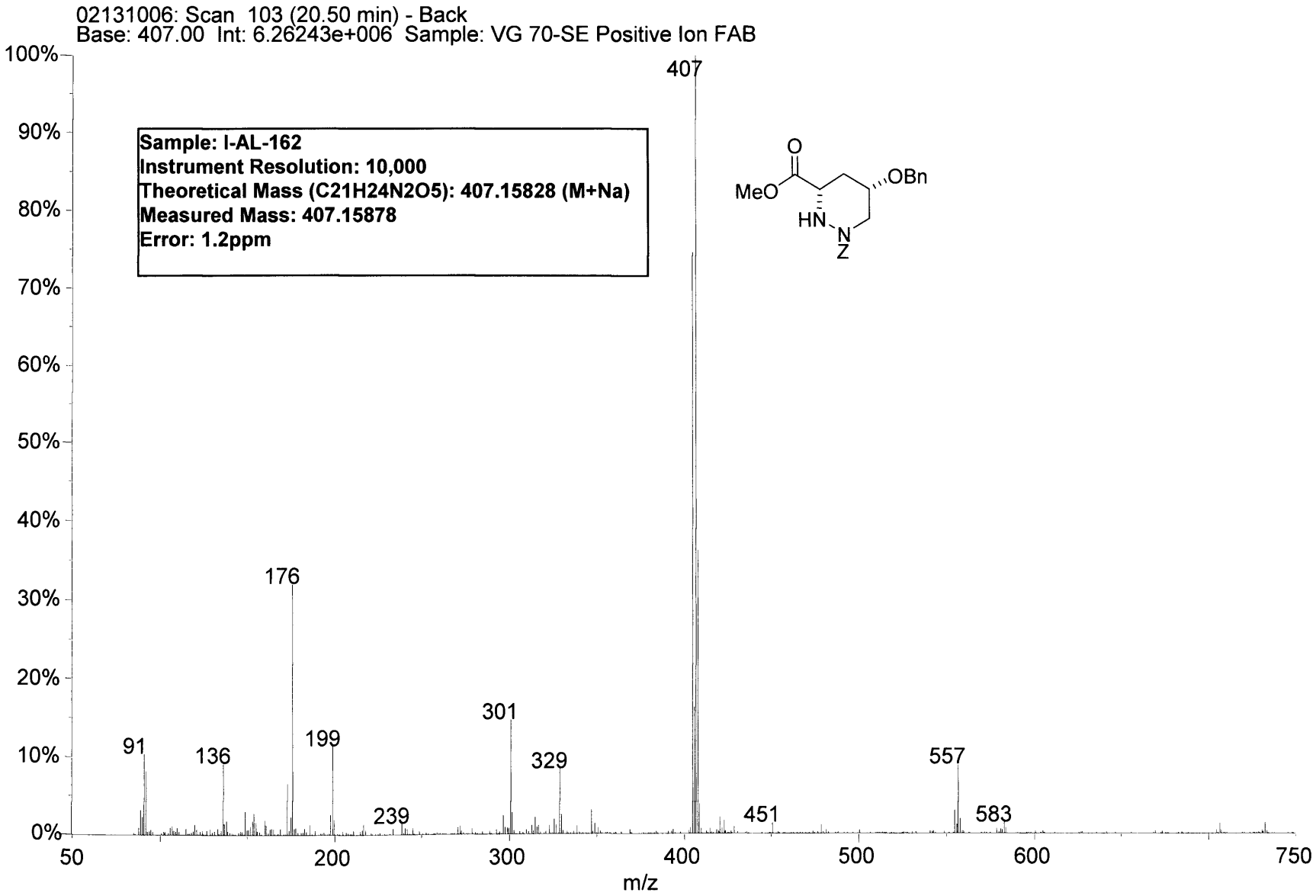
I-AL-162-1
COSY
C6D6 - 298K

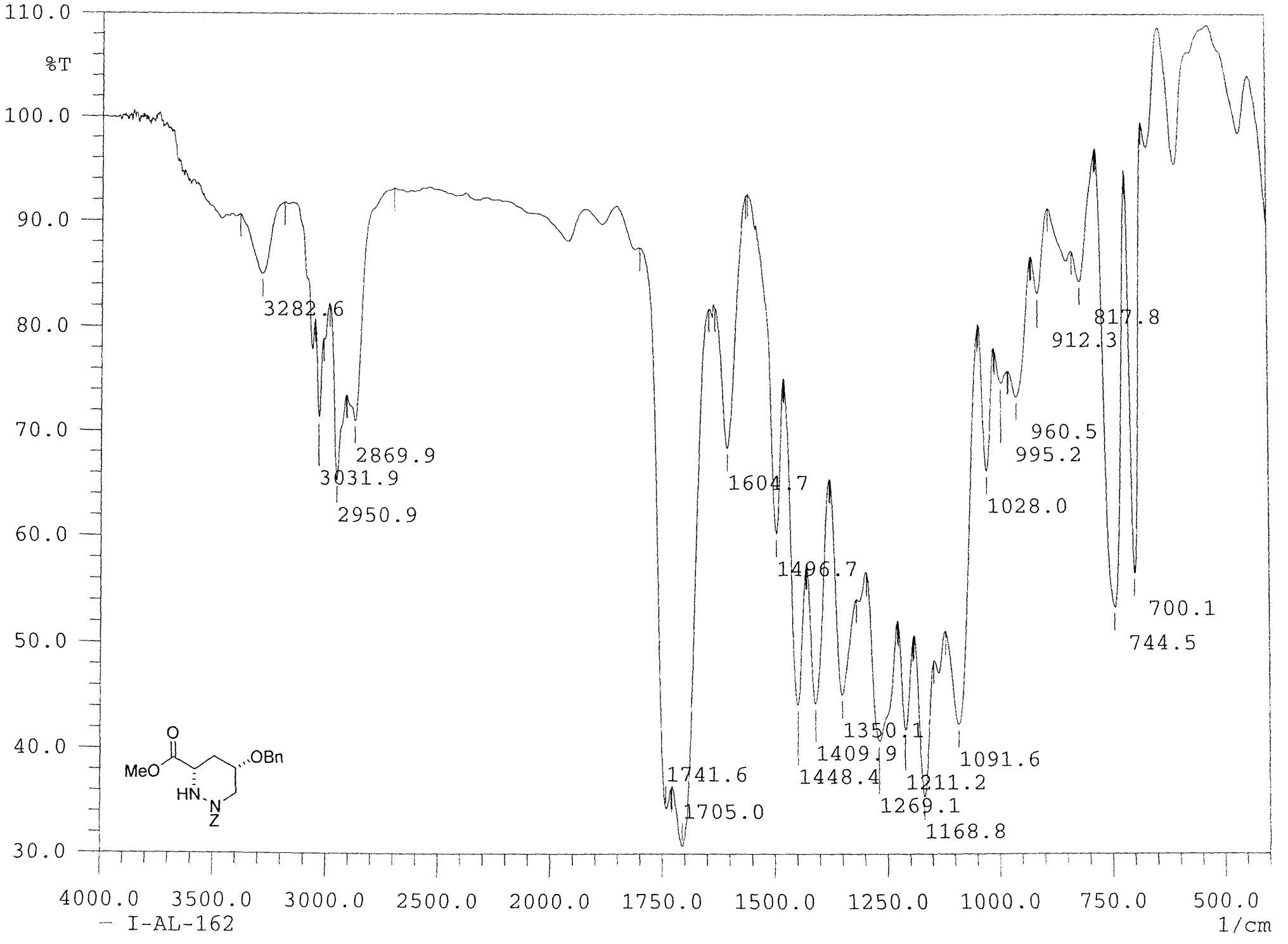


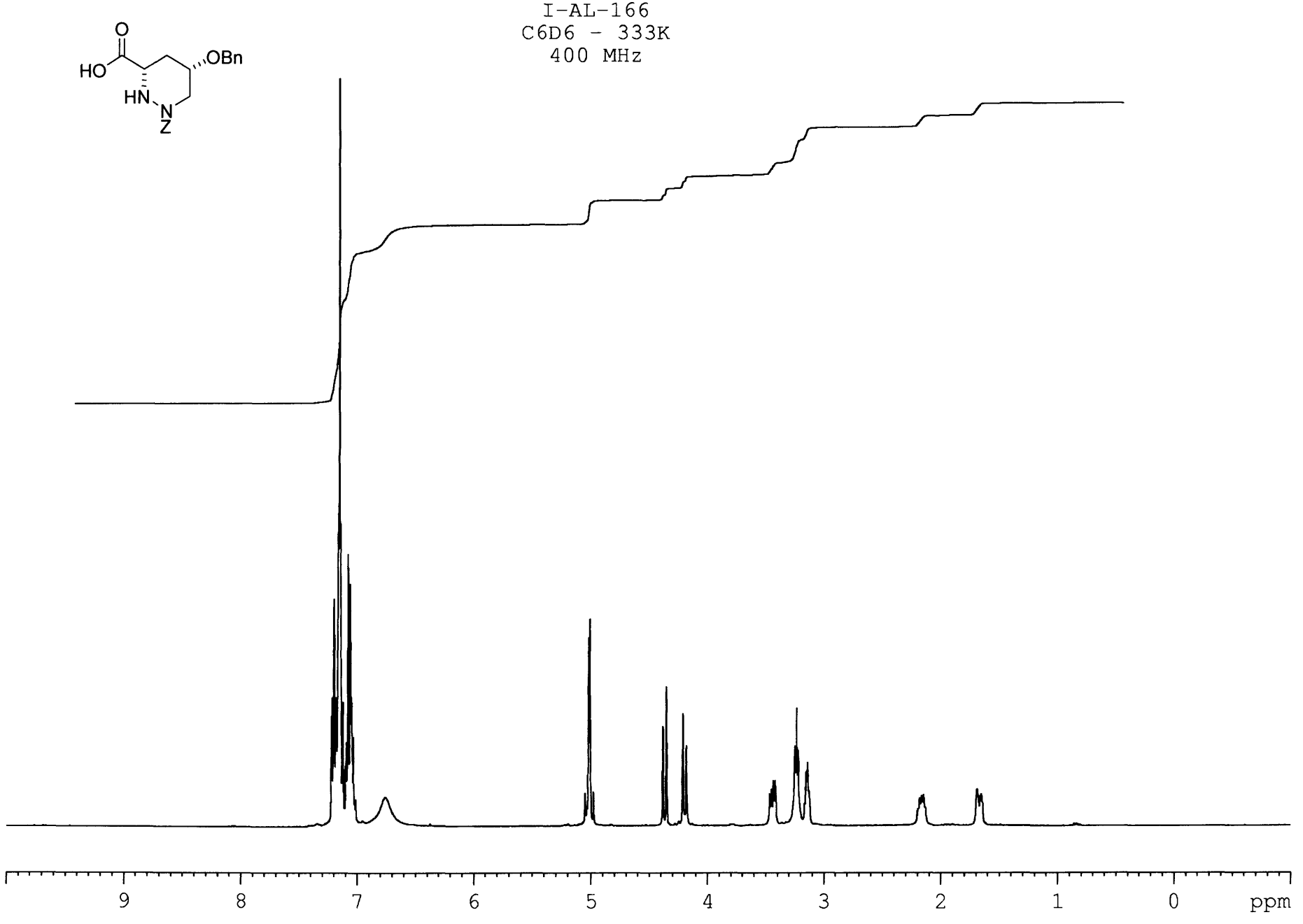


I-AL-162-1
HMQC
C6D6 - 298K

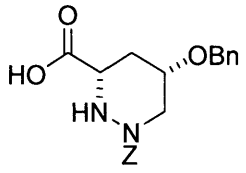


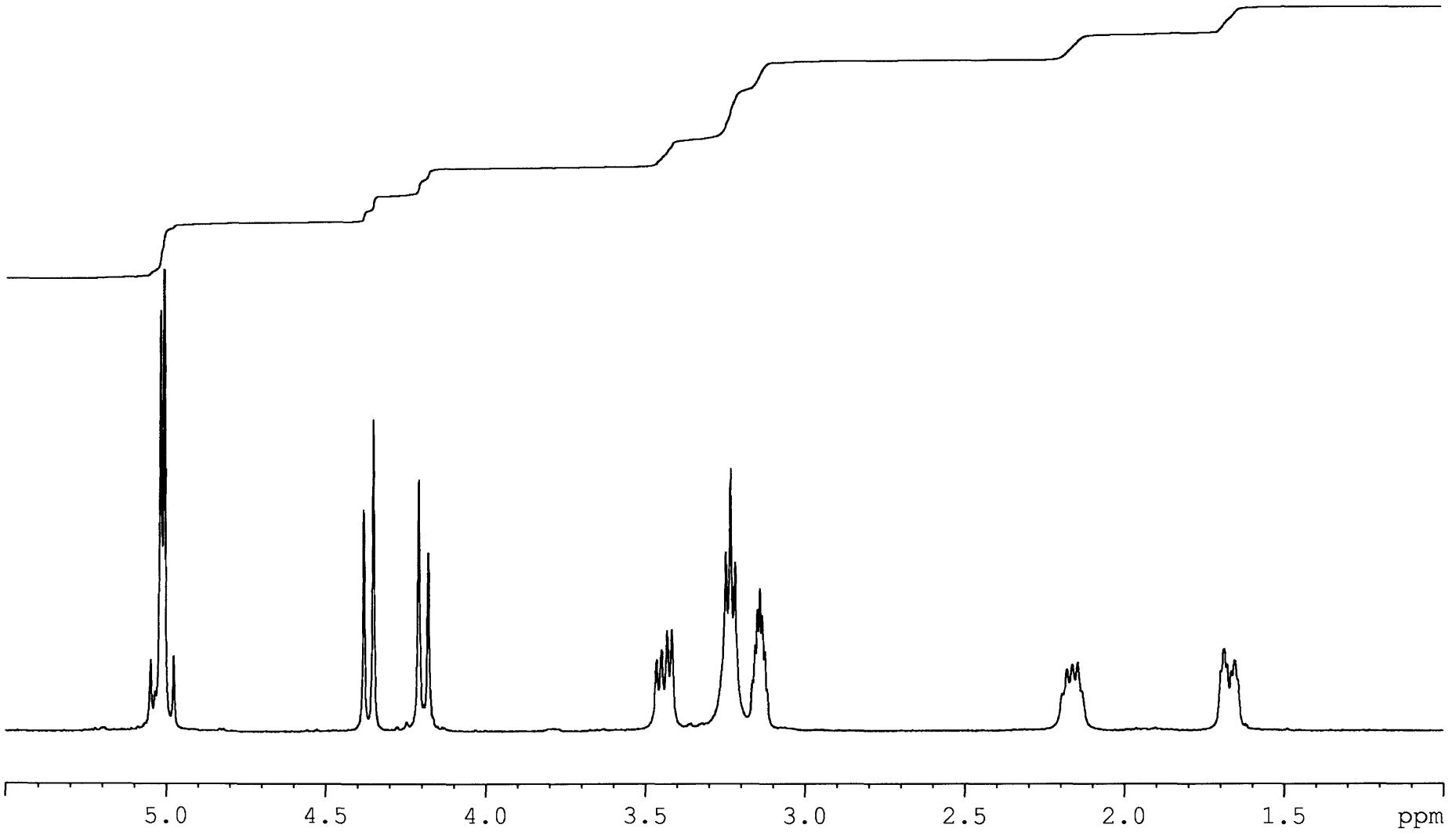

02131006: Scan 103 (20.50 min) - Back
Base: 407.00 Int: 6.26243e+006 Sample: VG 70-SE Positive Ion FAB
Sample: I-AL-162
Instrument Resolution: 10,000
Theoretical Mass (C21H24N2O5): 407.15828 (M+Na)
Measured Mass: 407.15878
Error: 1.2ppm
MeO
O
OBn
HN
N
Z
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
407
176
301
199
91
136
329
557
239
451
583
50
200
300
400
500
600
750
m/z

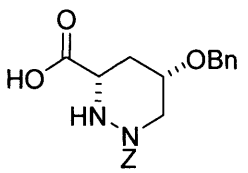

110.0
%T
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
3282.6
2869.9
3031.9
2950.9
1604.7
1496.7
1741.6
1705.0
1448.4
1409.9
1350.1
1269.1
1211.2
1168.8
1091.6
1028.0
995.2
960.5
912.3
817.8
744.5
700.1
MeO
OBn
HN
N
Z
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
- I-AL-162
1/cm


I-AL-166
C6D6 - 333K
400 MHz
O
HO
OBn
HN
N
Z
9
8
7
6
5
4
3
2
1
0
ppm

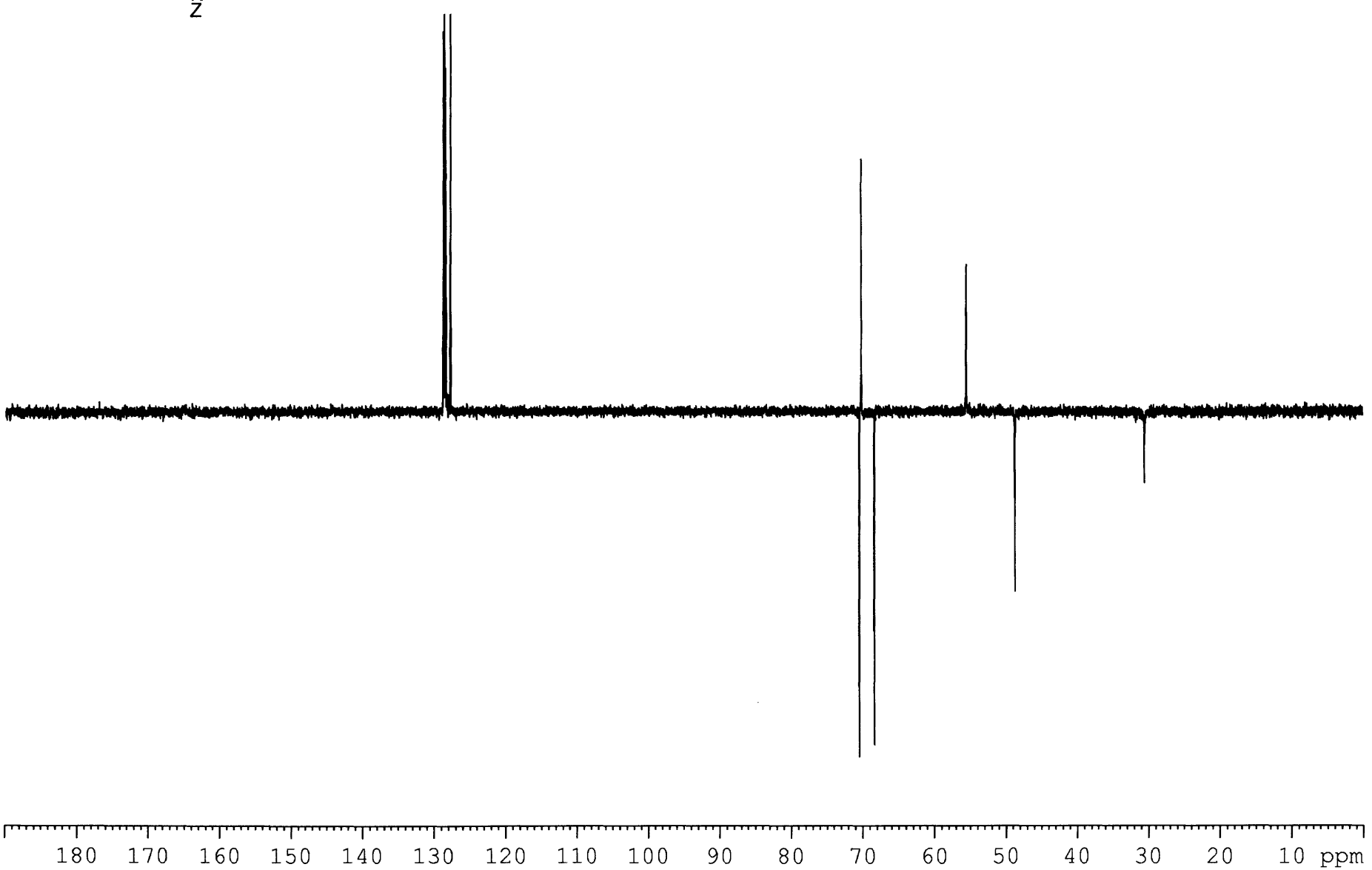
I-AL-166
C6D6 - 333K
400 MHz



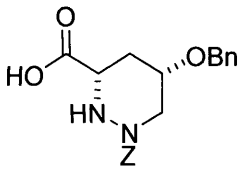


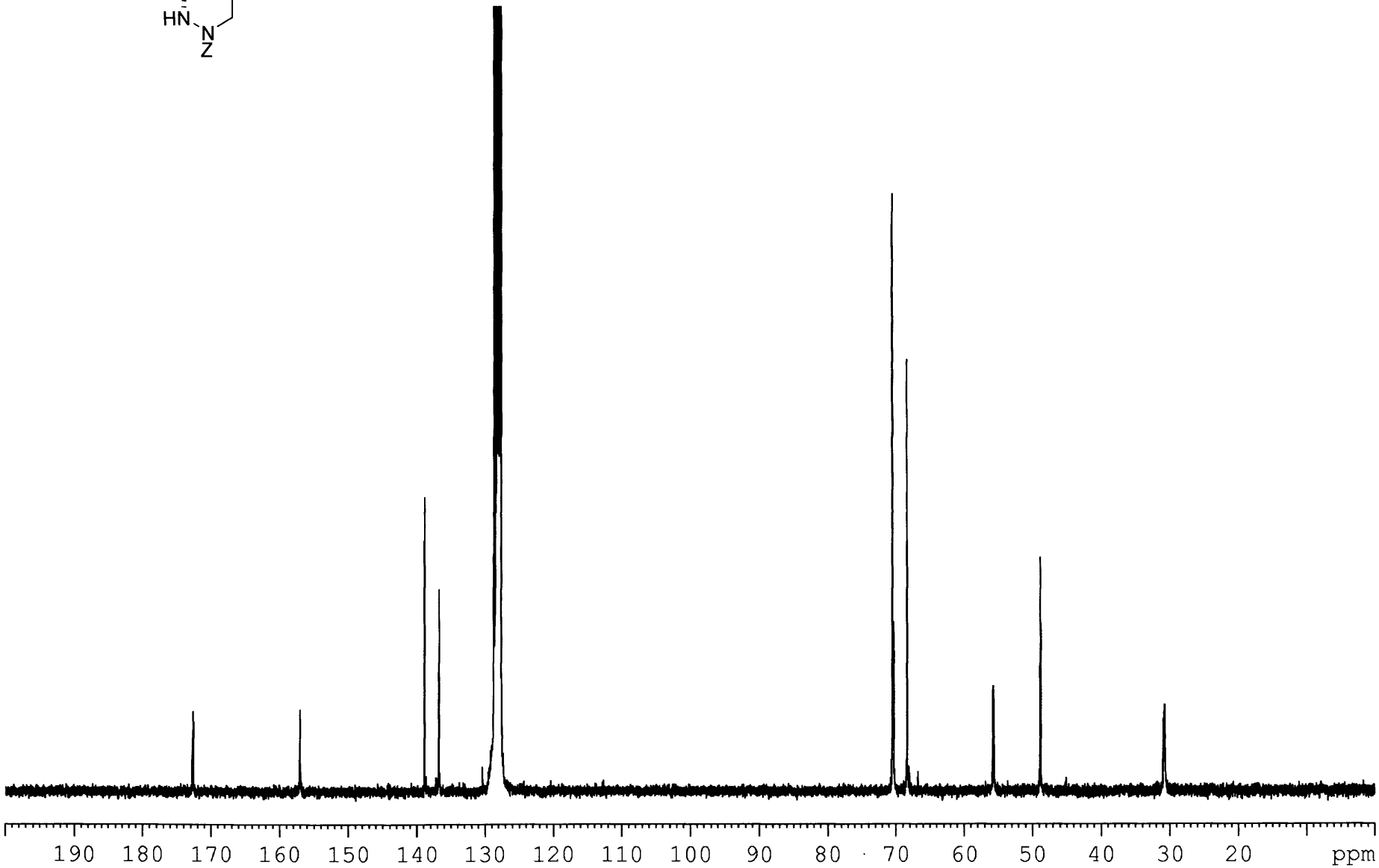


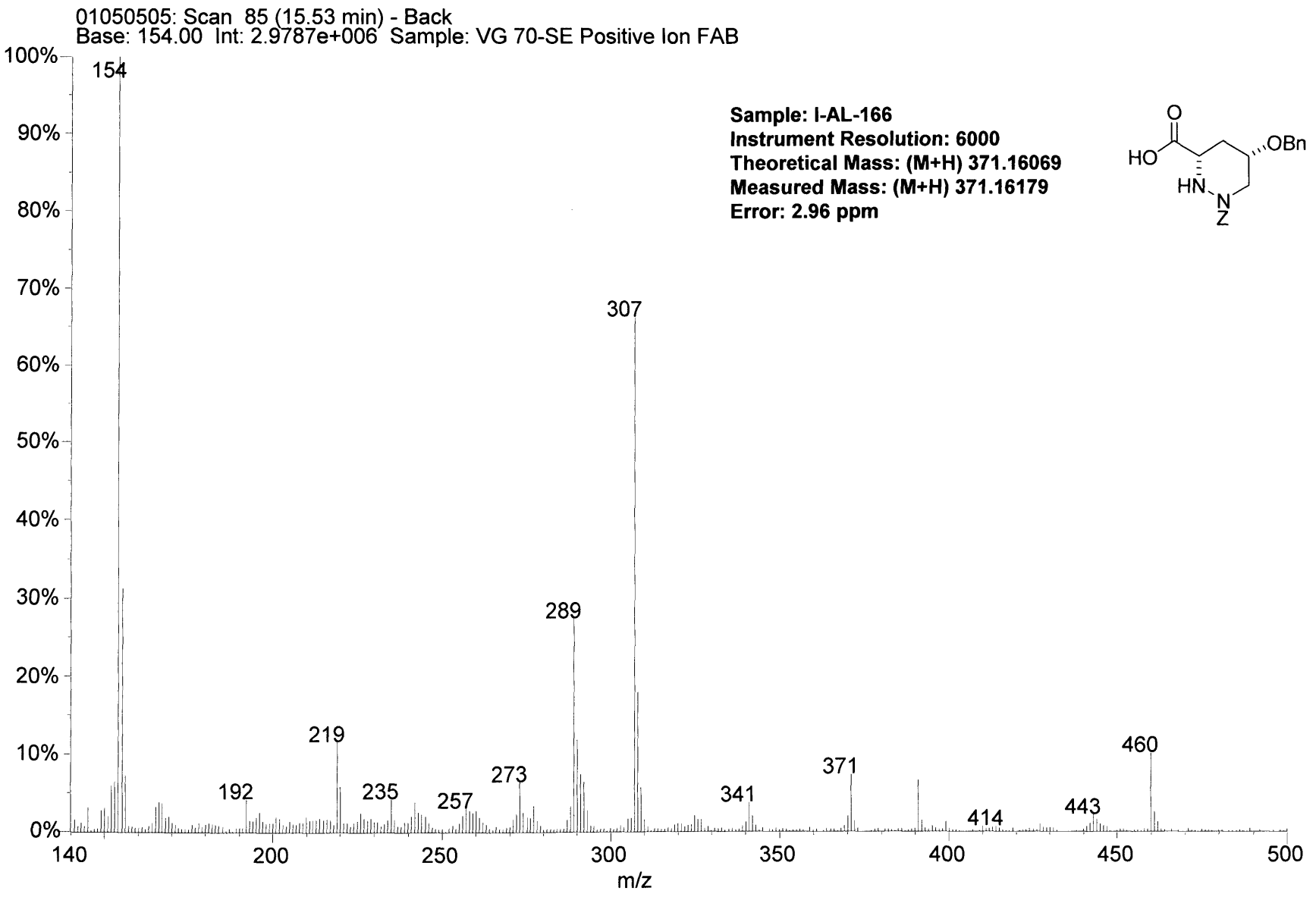
I-AL-166
dept
C6D6 - 333K

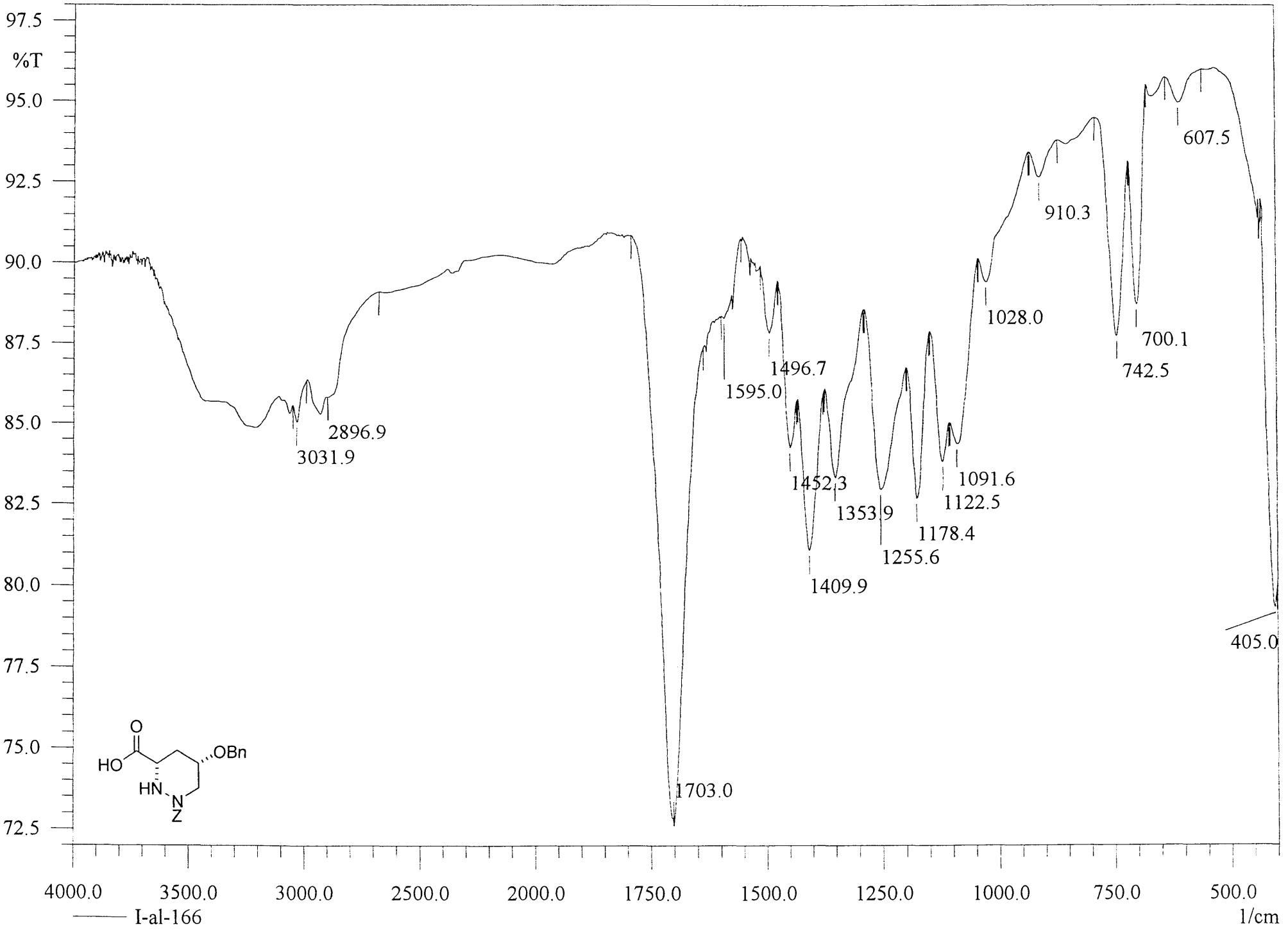


I-AL-166
13C
C6D6 - 333K

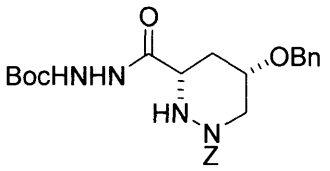




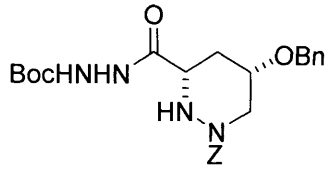

01050505: Scan 85 (15.53 min) - Back
Base: 154.00 Int: 2.9787e+006 Sample: VG 70-SE Positive Ion FAB
Sample: I-AL-166
Instrument Resolution: 6000
Theoretical Mass: (M+H) 371.16069
Measured Mass: (M+H) 371.16179
Error: 2.96 ppm
O
HO
OBn
HN
N
Z
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
154
307
289
219
192
235
257
273
341
371
414
443
460
140
200
250
300
350
400
450
500
m/z


97.5
%T
95.0
92.5
90.0
87.5
85.0
82.5
80.0
77.5
75.0
72.5
3031.9
2896.9
1595.0
1496.7
1452.3
1409.9
1353.9
1255.6
1178.4
1122.5
1091.6
1028.0
910.3
742.5
700.1
607.5
405.0
1703.0
HO
O
HN
N
Z
OBn
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
I-al-166

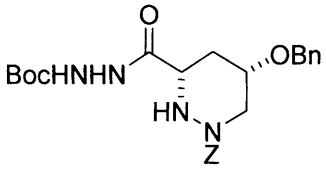
I-AL-172
C6D6 - 333K

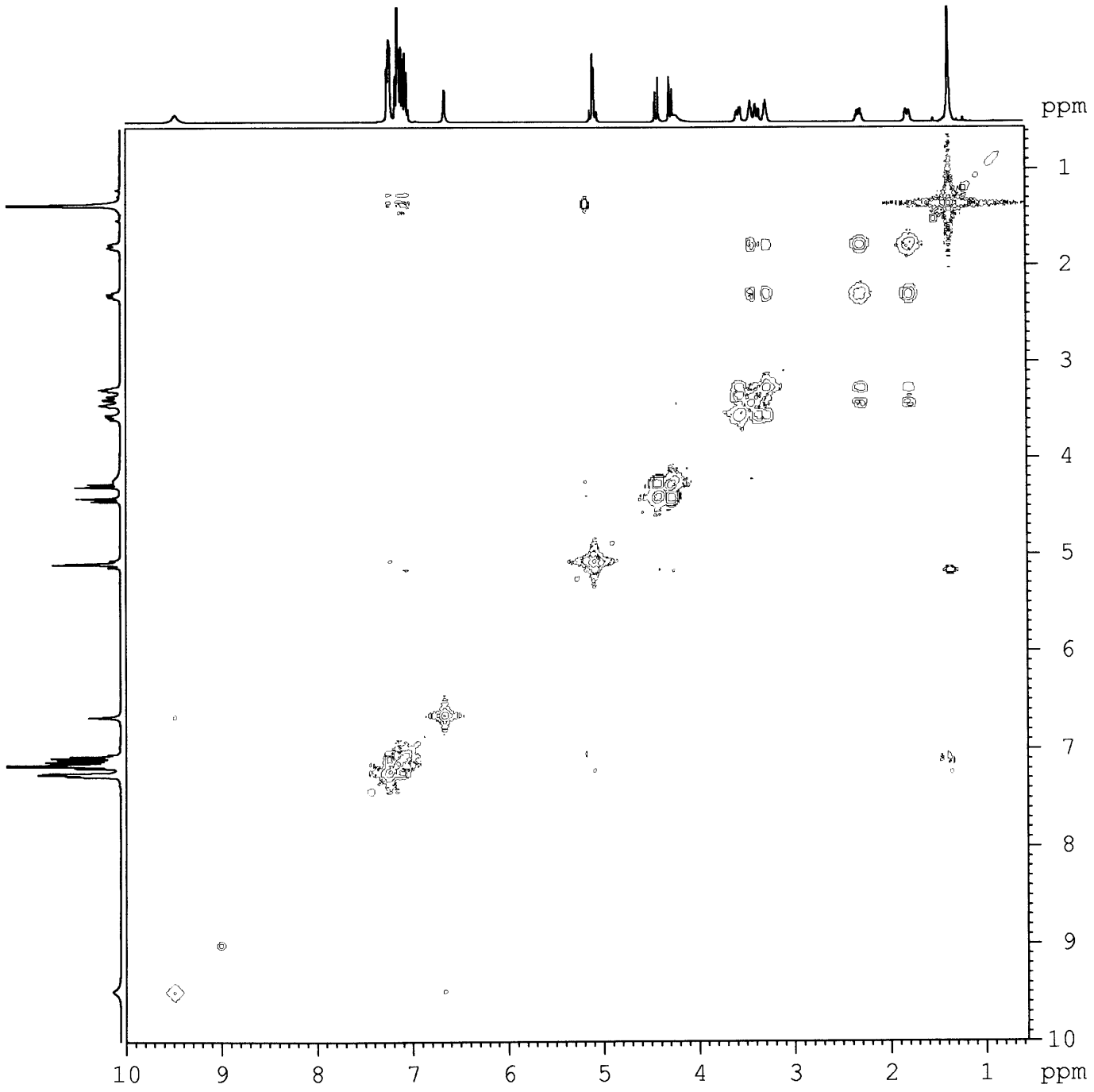


I-AL-172
dept
C6D6 - 333K

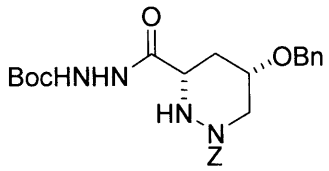


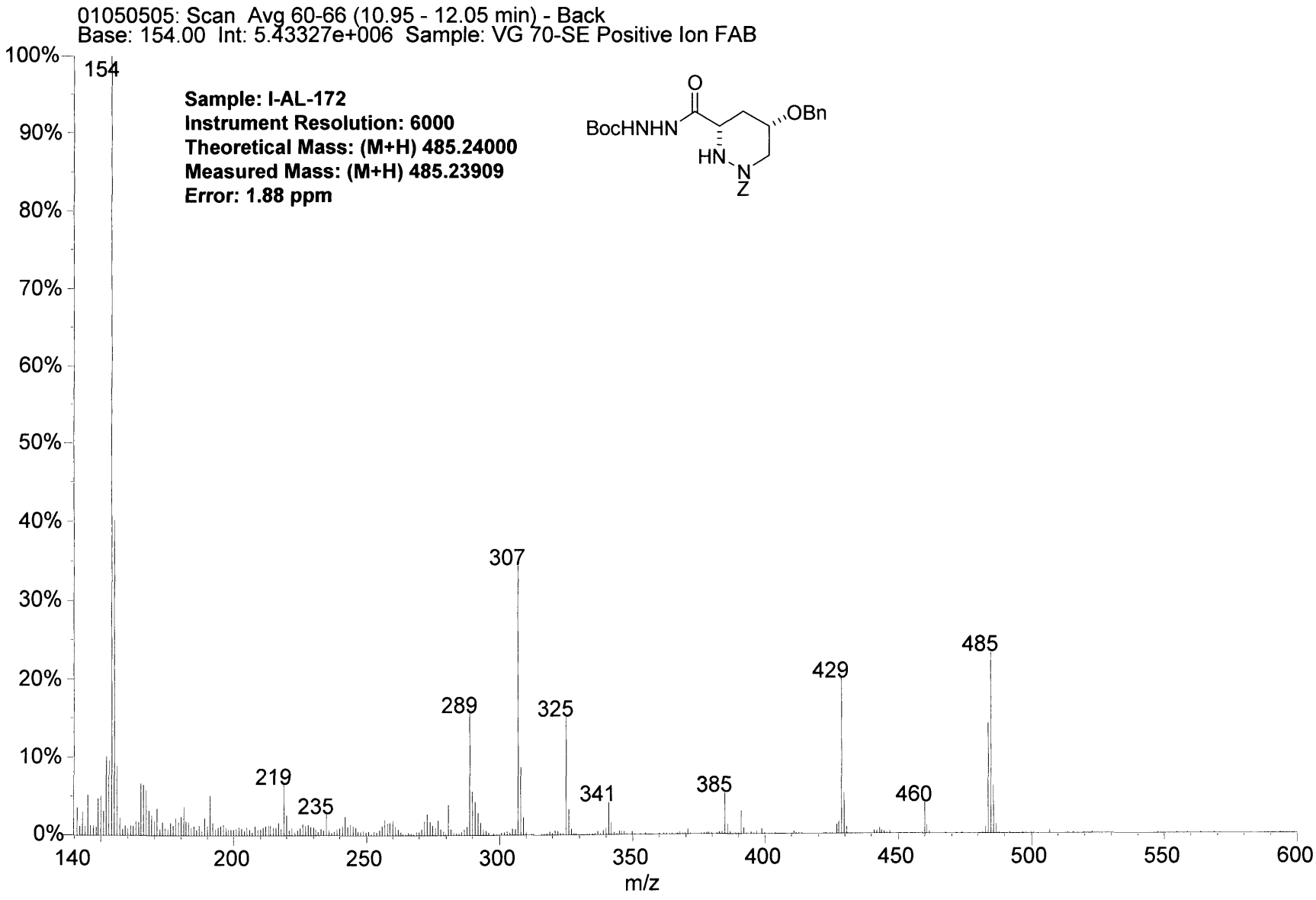
I-AL-172
13C
C6D6 - 333K

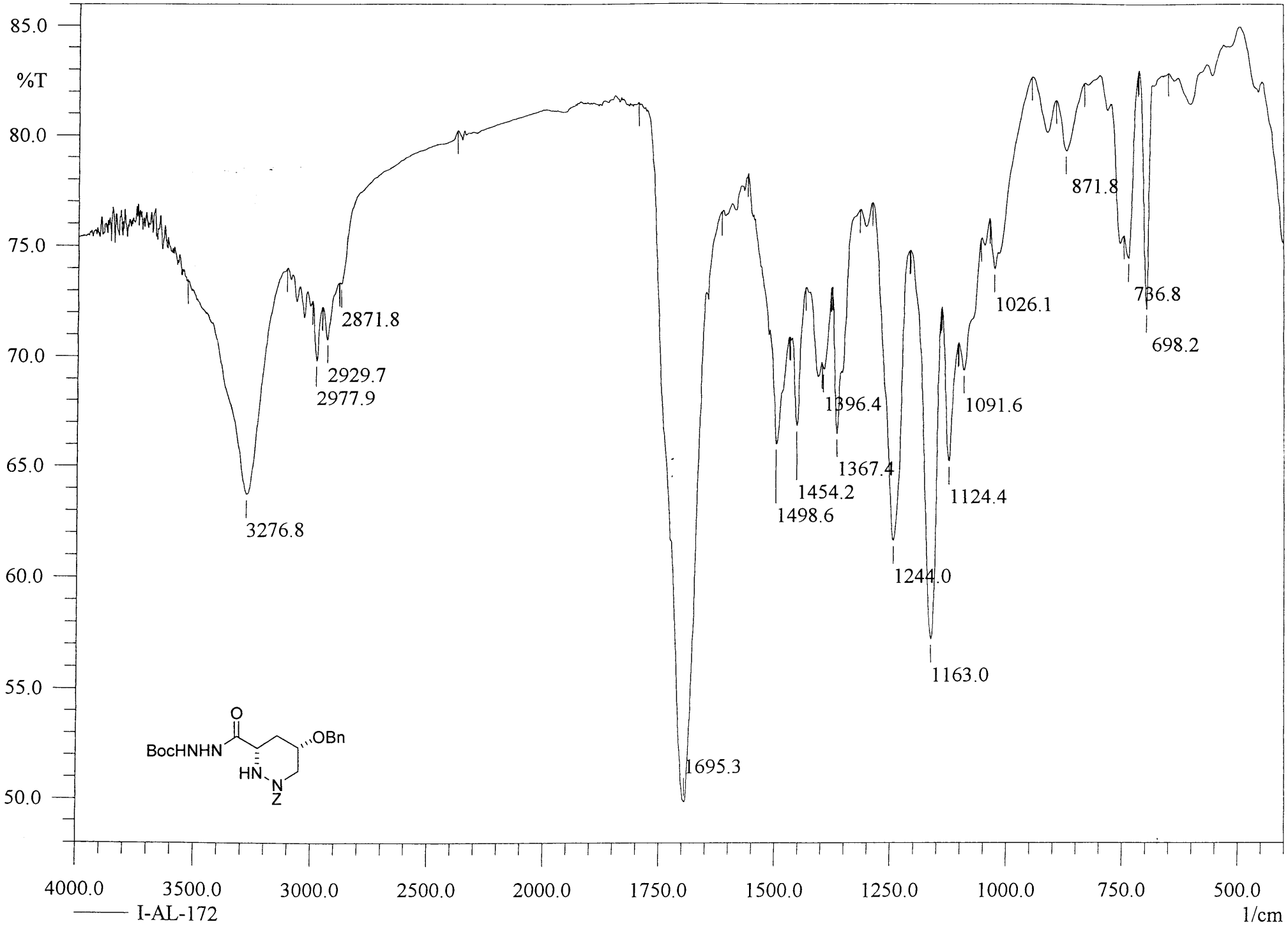




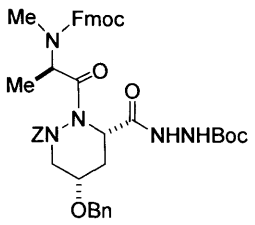
I-AL-172
cosy
C6D6 - 333K

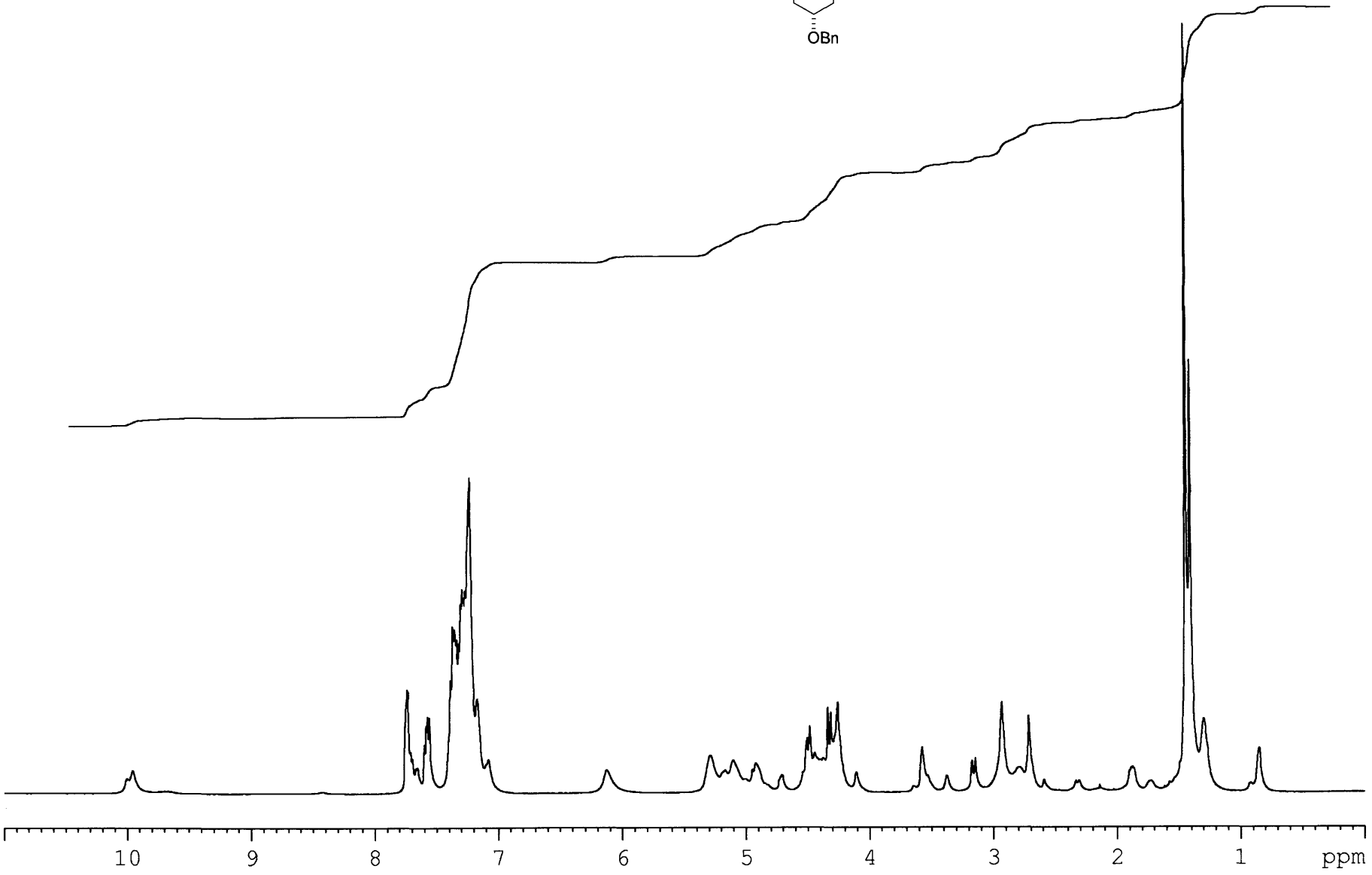



01050505: Scan Avg 60-66 (10.95 - 12.05 min) - Back
Base: 154.00 Int: 5.43327e+006 Sample: VG 70-SE Positive Ion FAB
Sample: I-AL-172
Instrument Resolution: 6000
Theoretical Mass: (M+H) 485.24000
Measured Mass: (M+H) 485.23909
Error: 1.88 ppm
BocHNHN
O
OBn
HN
N
Z
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
154
307
289
325
219
235
341
385
429
460
485
140
200
250
300
350
400
450
500
550
600
m/z

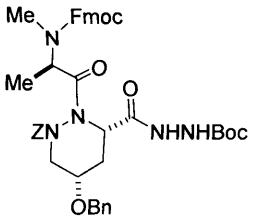

85.0
%T
80.0
75.0
70.0
65.0
60.0
55.0
50.0
3276.8
2871.8
2929.7
2977.9
1695.3
1498.6
1454.2
1396.4
1367.4
1244.0
1163.0
1124.4
1091.6
1026.1
871.8
736.8
698.2
BocHNHN
O
OBn
HN
N
Z
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
I-AL-172

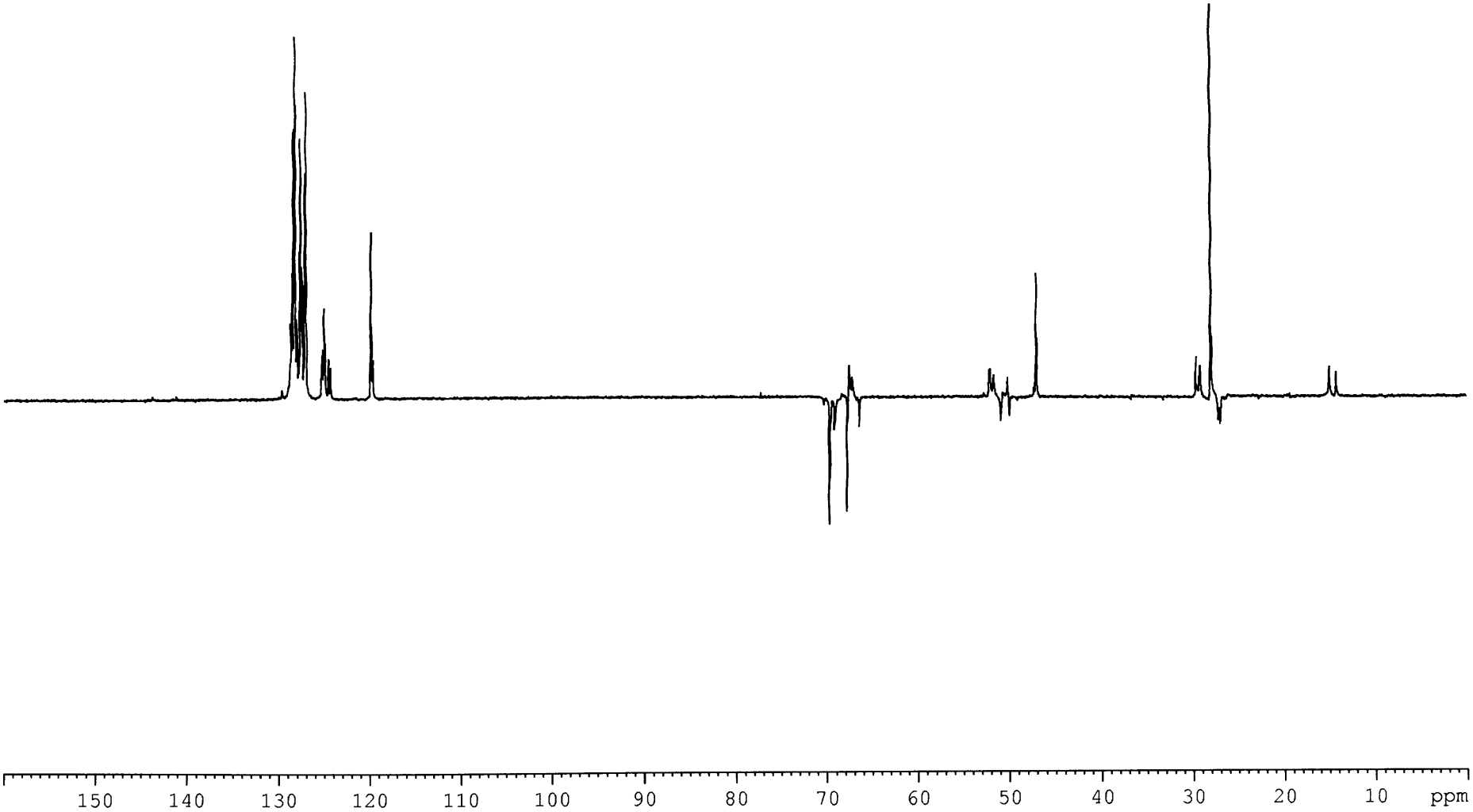
II-AL-38
CDCl3 - 298K



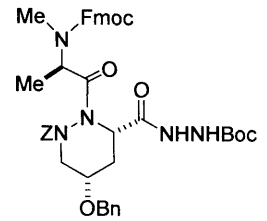


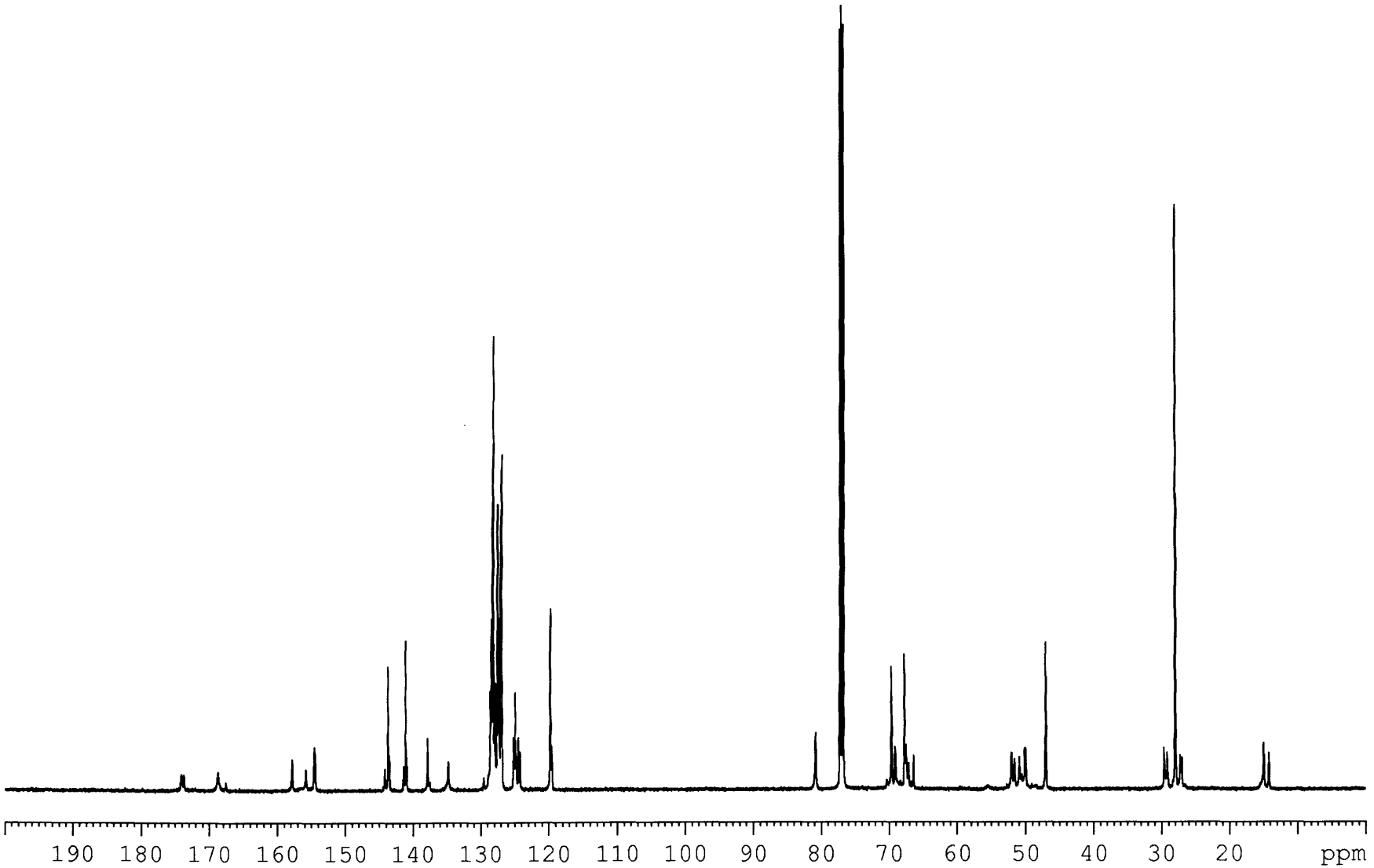
II-AL-38
Dept
CDCl3 - 298K

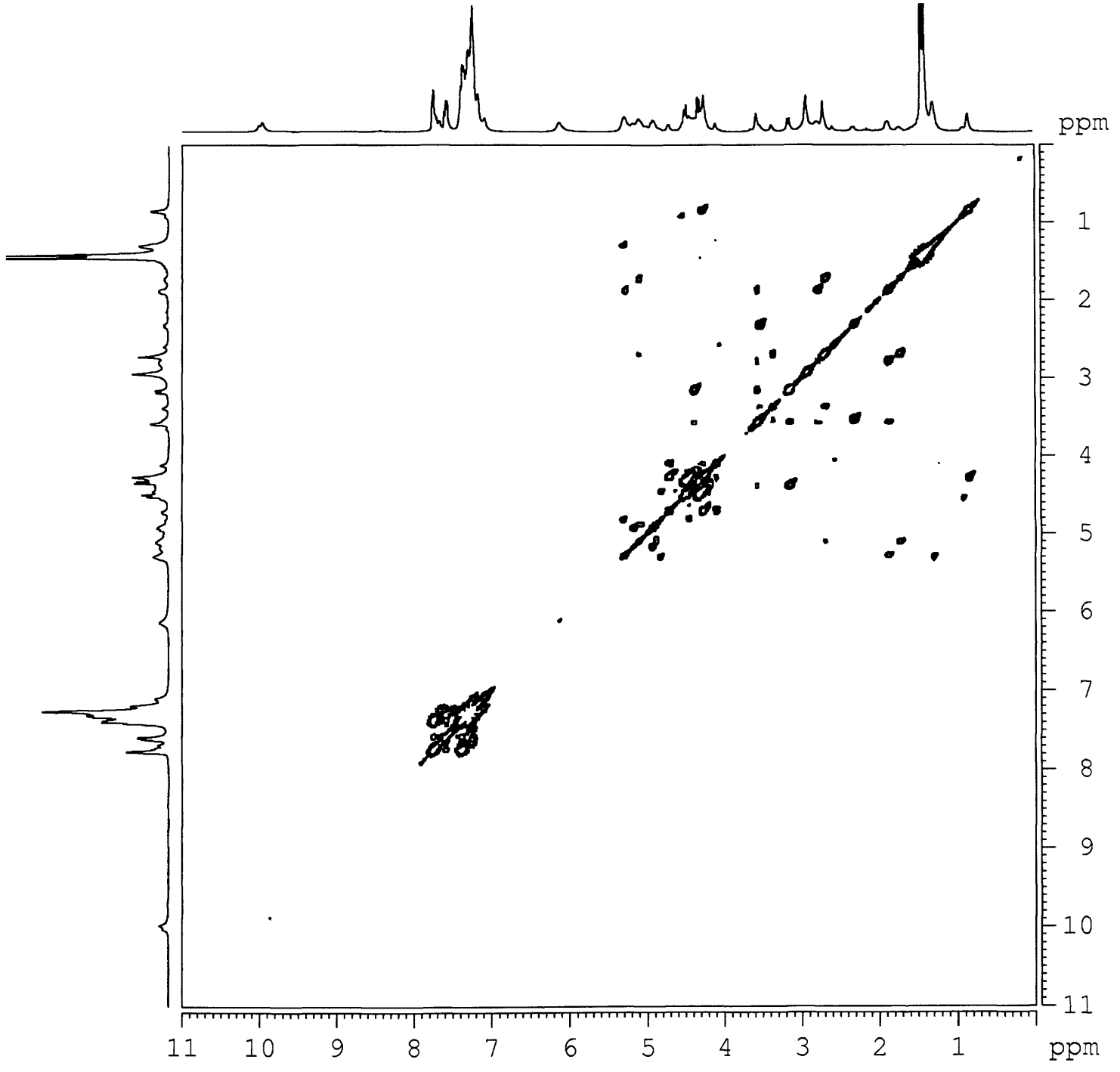




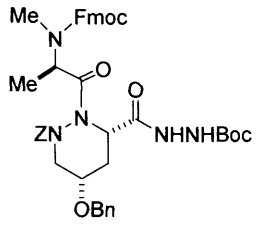
II-AL-38
13C
CDCl3 - 298K



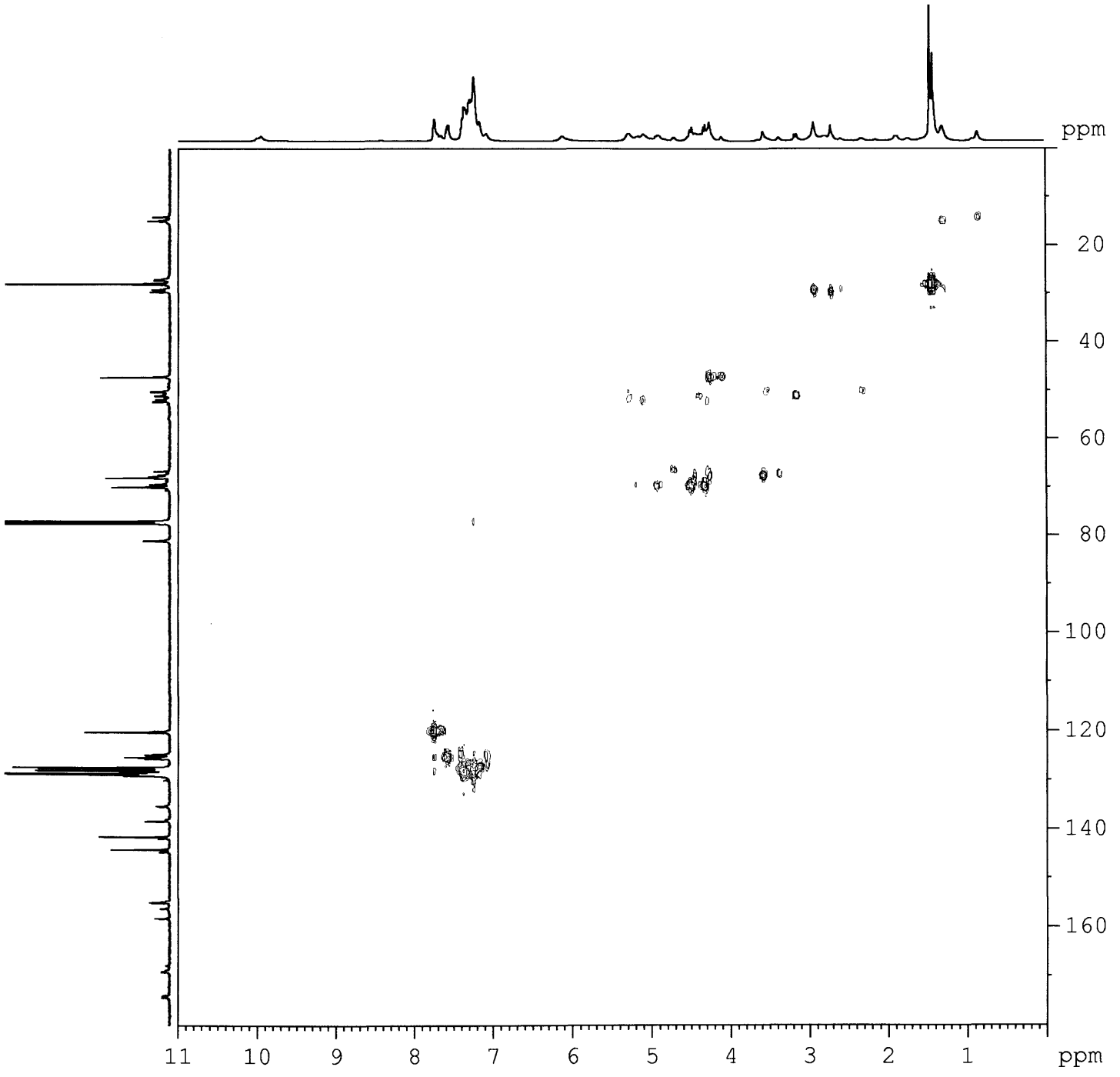


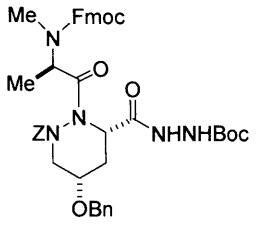


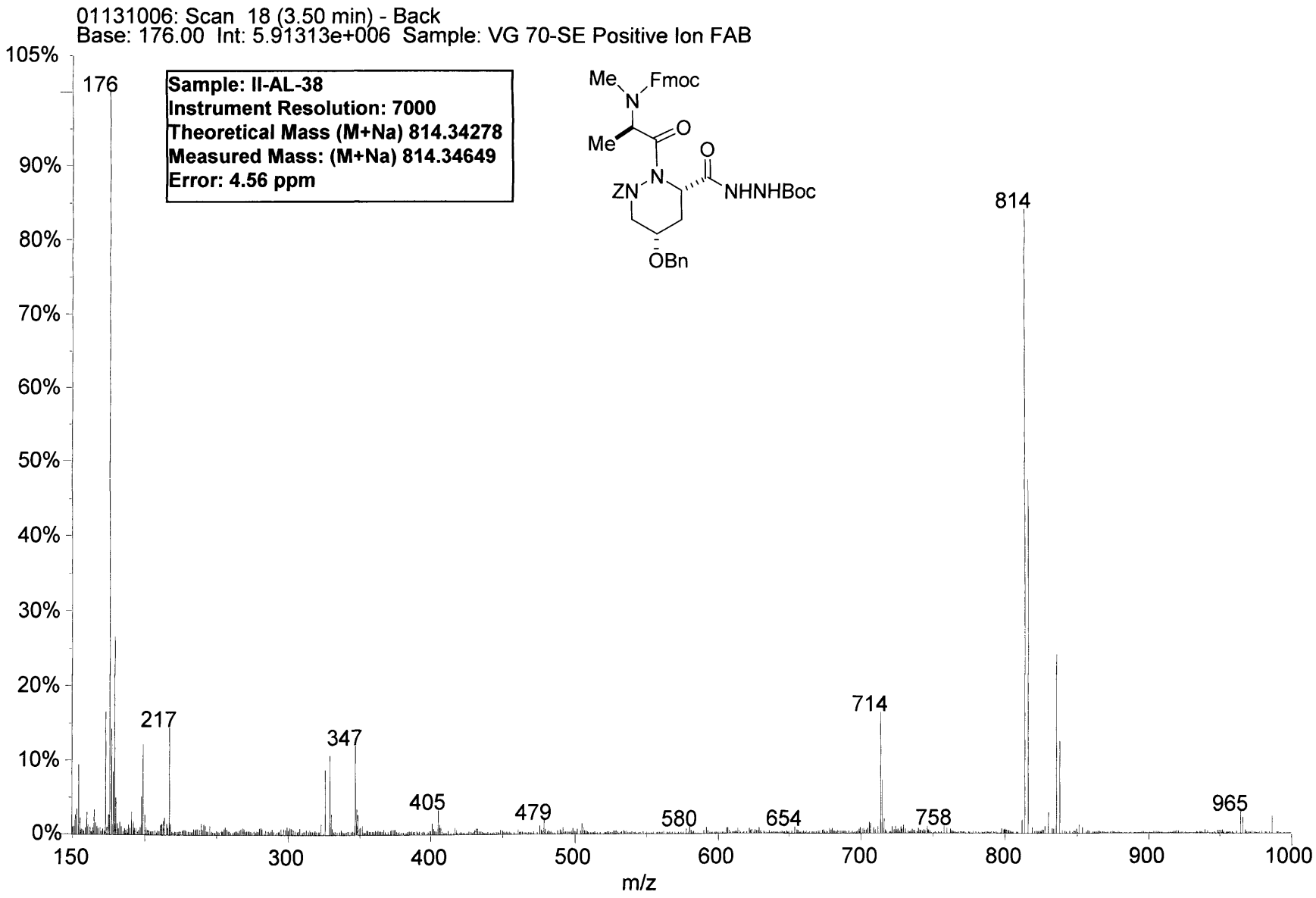
II-AL-38
COSY
CDCl3 - 298K
500MHz

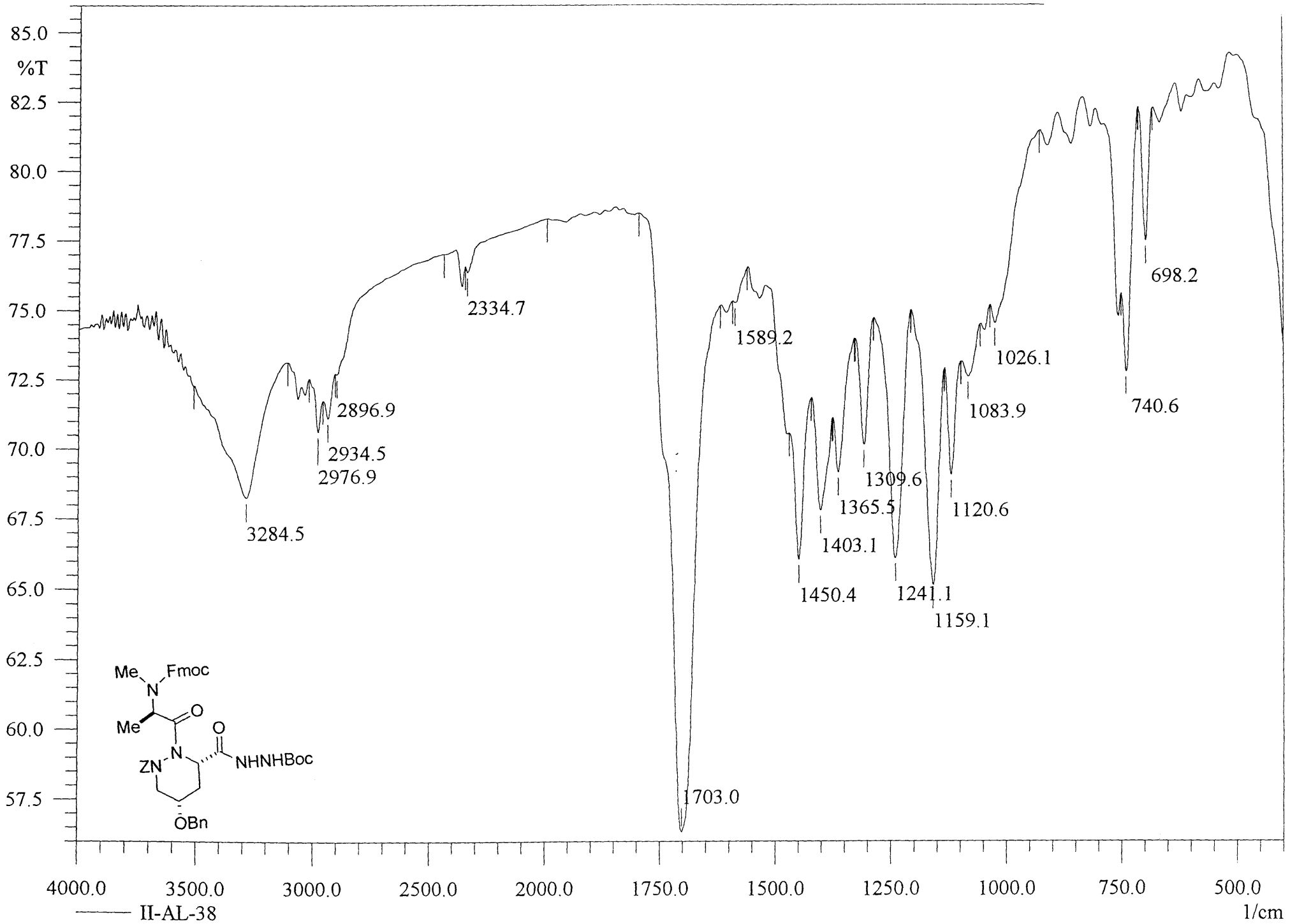


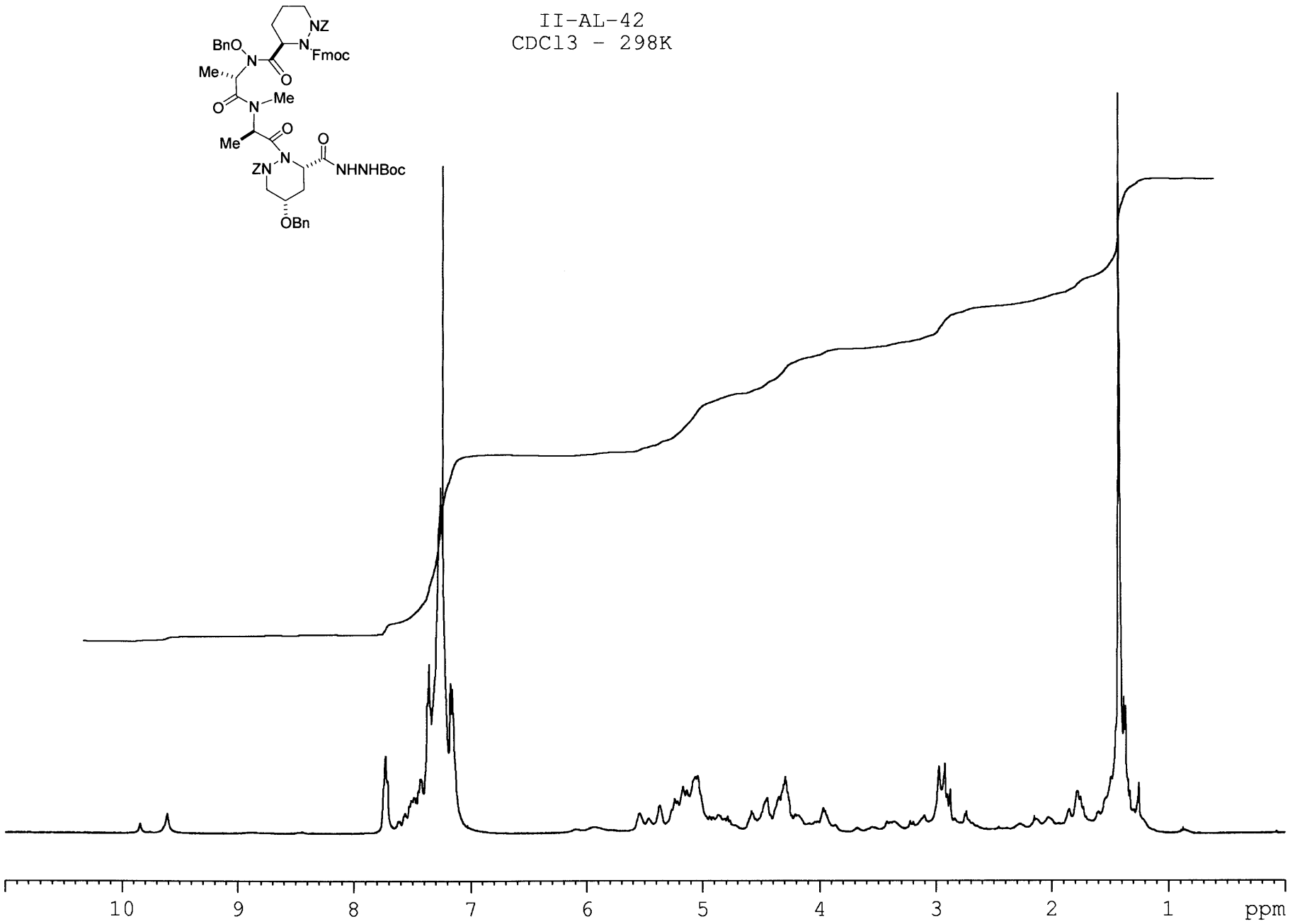
II-AL-38
HMQC
CDCl3 - 298K



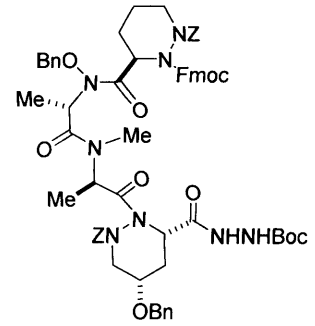


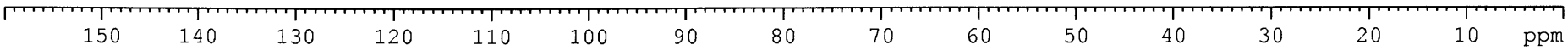

01131006: Scan 18 (3.50 min) - Back
Base: 176.00 Int: 5.91313e+006 Sample: VG 70-SE Positive Ion FAB
Sample: II-AL-38
Instrument Resolution: 7000
Theoretical Mass (M+Na) 814.34278
Measured Mass: (M+Na) 814.34649
Error: 4.56 ppm
Me
Fmoc
N
Me
O
O
ZN
N
NHNHBoc
OBn
105%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
176
217
347
405
479
580
654
714
758
814
965
150
300
400
500
600
700
800
900
1000
m/z

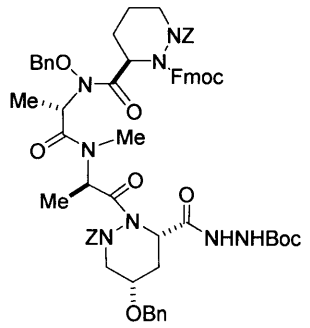

85.0
%T
82.5
80.0
77.5
75.0
72.5
70.0
67.5
65.0
62.5
60.0
57.5
3284.5
2896.9
2934.5
2976.9
2334.7
1589.2
1703.0
1450.4
1403.1
1365.5
1309.6
1241.1
1159.1
1120.6
1083.9
1026.1
740.6
698.2
Me
Fmoc
N
O
Me
O
ZN
N
NHNHBoc
OBn
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
II-AL-38


II-AL-42
CDCl3 - 298K
BnO
N
Me
O
NZ
N
Fmoc
O
N
Me
O
Me
O
ZN
N
O
NHNHBoc
OBn
10
9
8
7
6
5
4
3
2
1
ppm

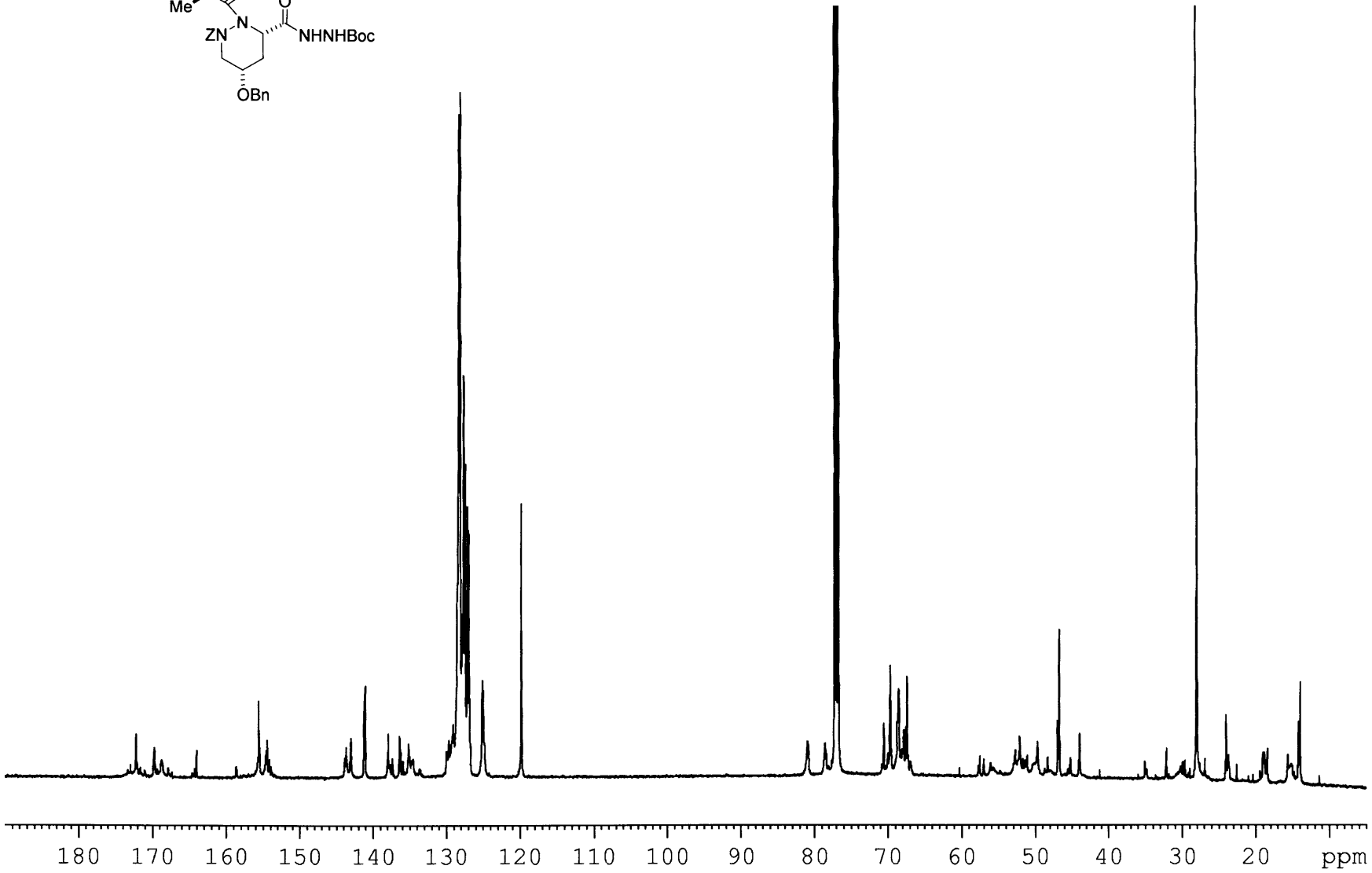
II-AL-42
DEPT
CDCl3 - 298K



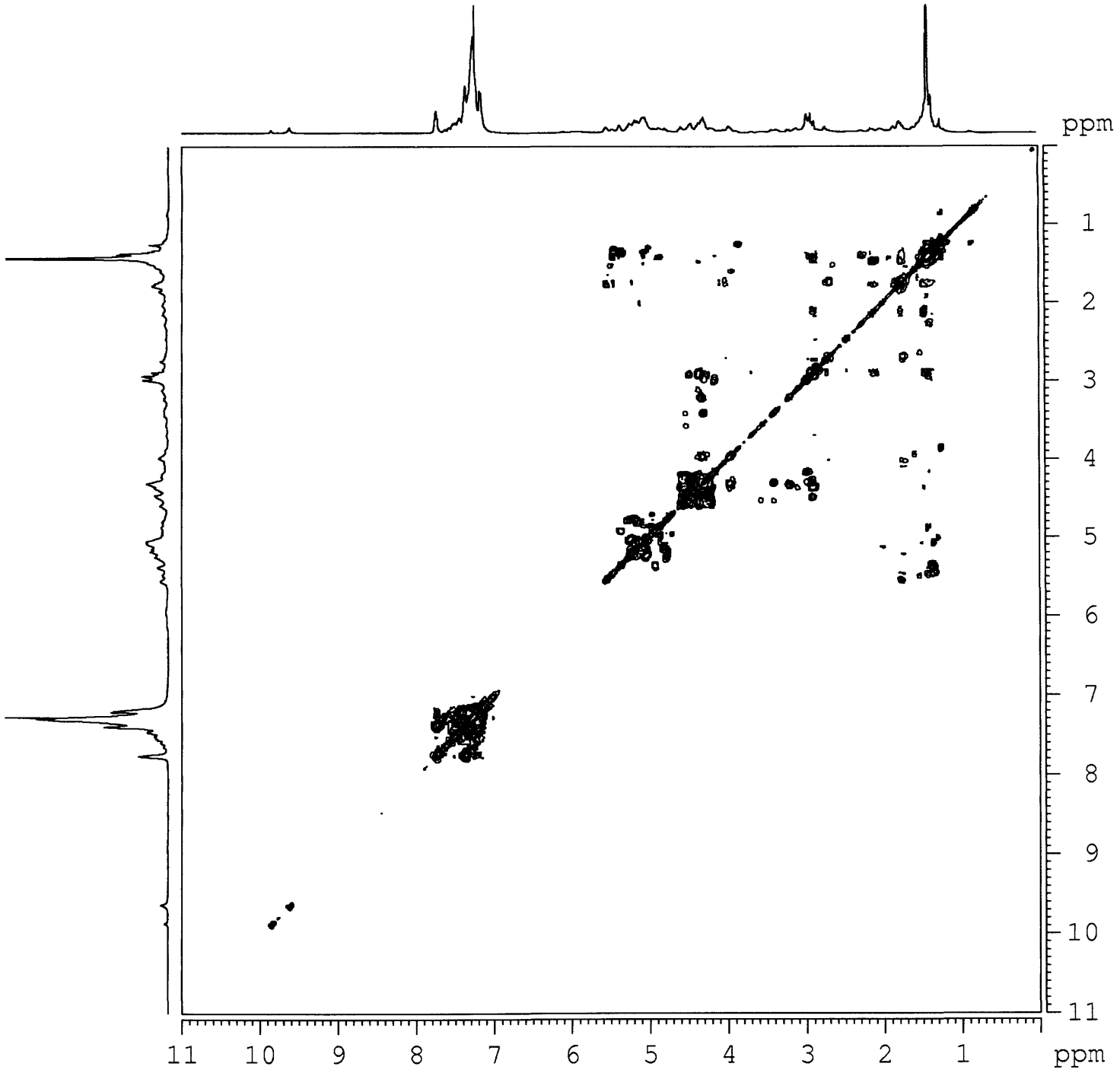


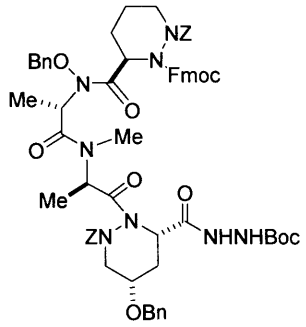


II-AL-42
13C
CDCl3 - 298K

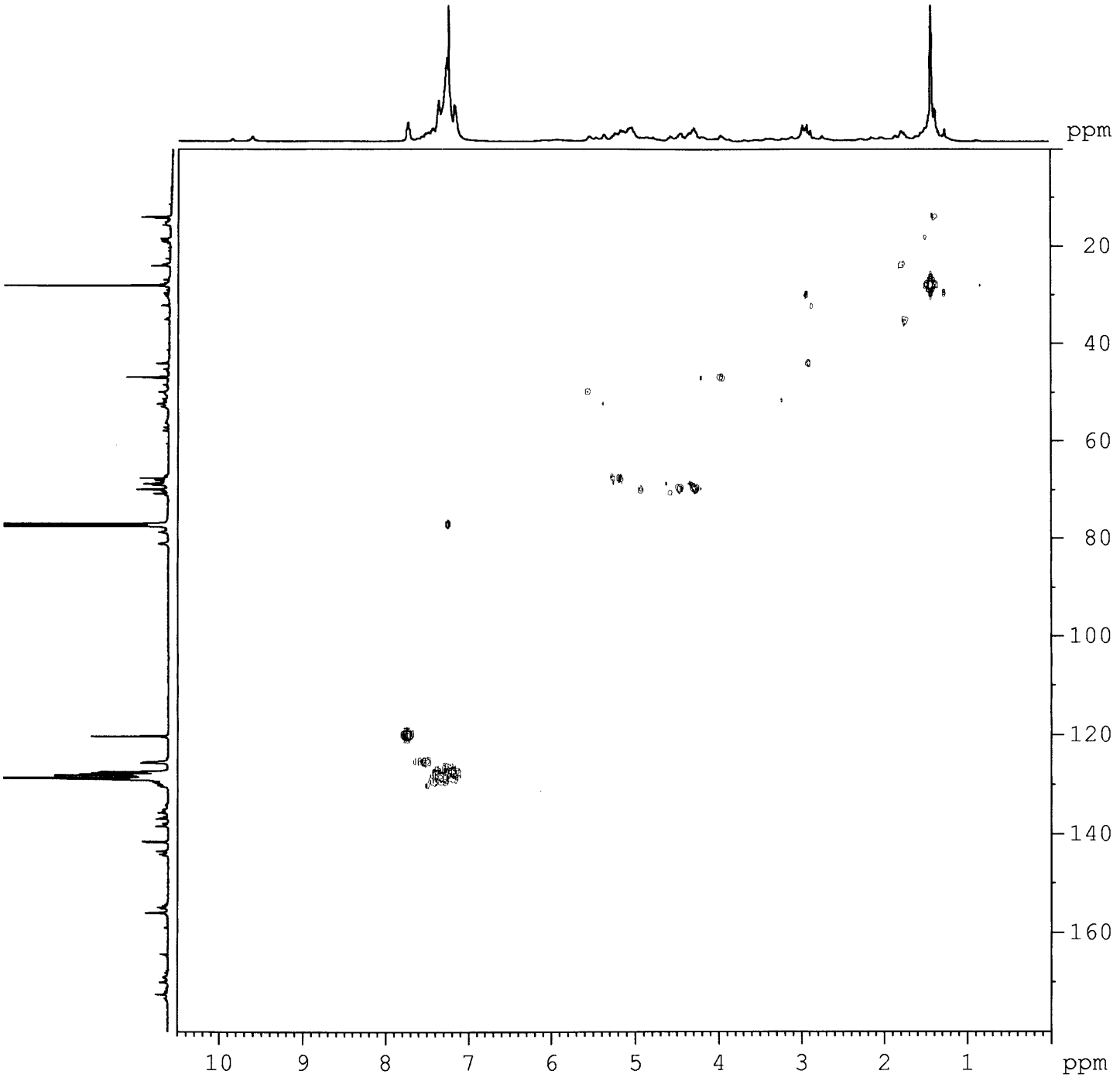


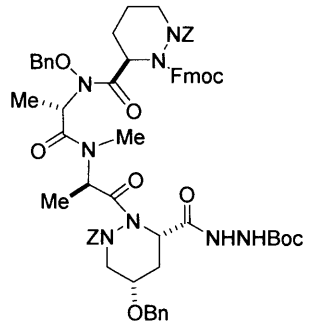
II-AL-42
COSY
CDCl3 - 298K

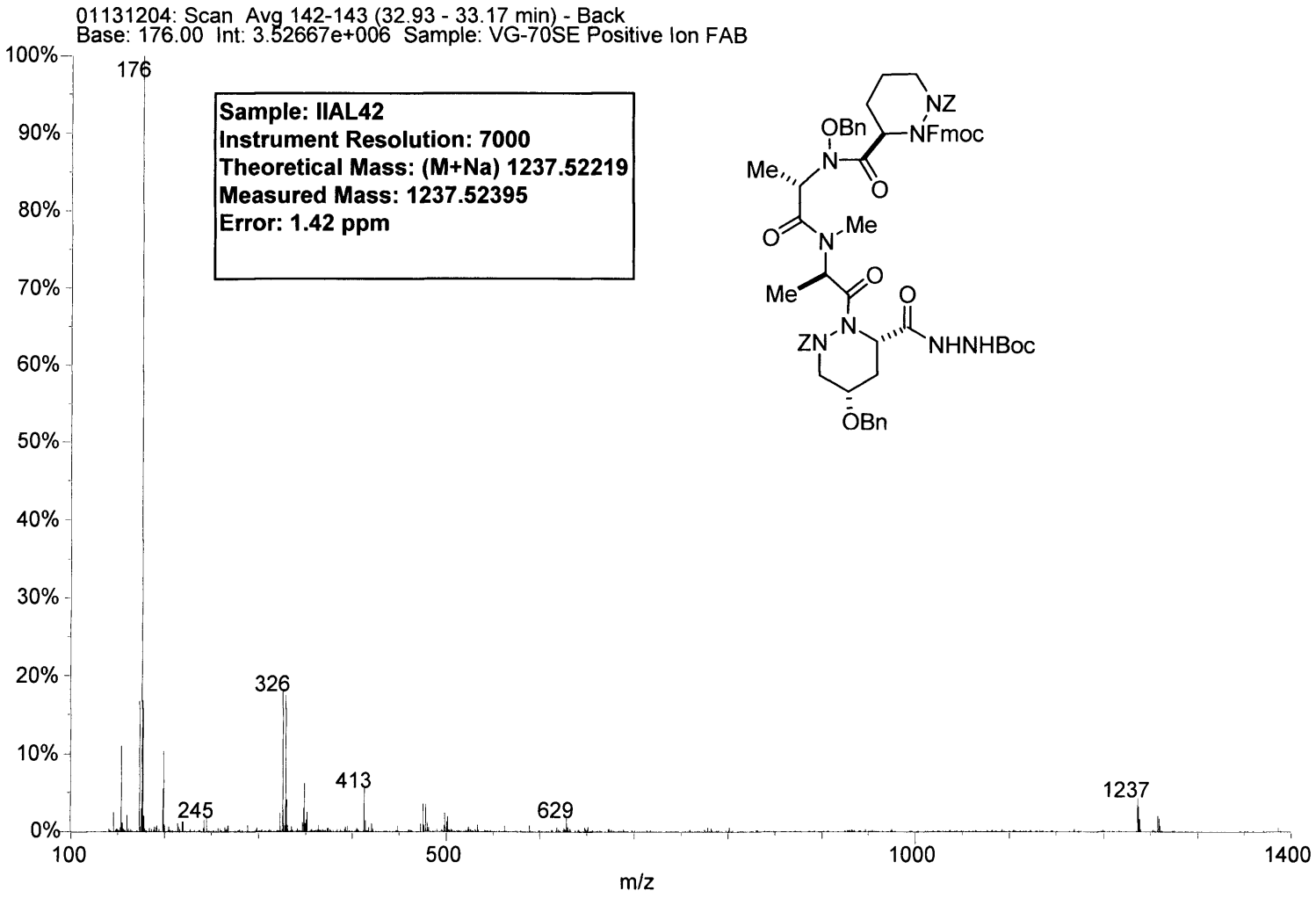


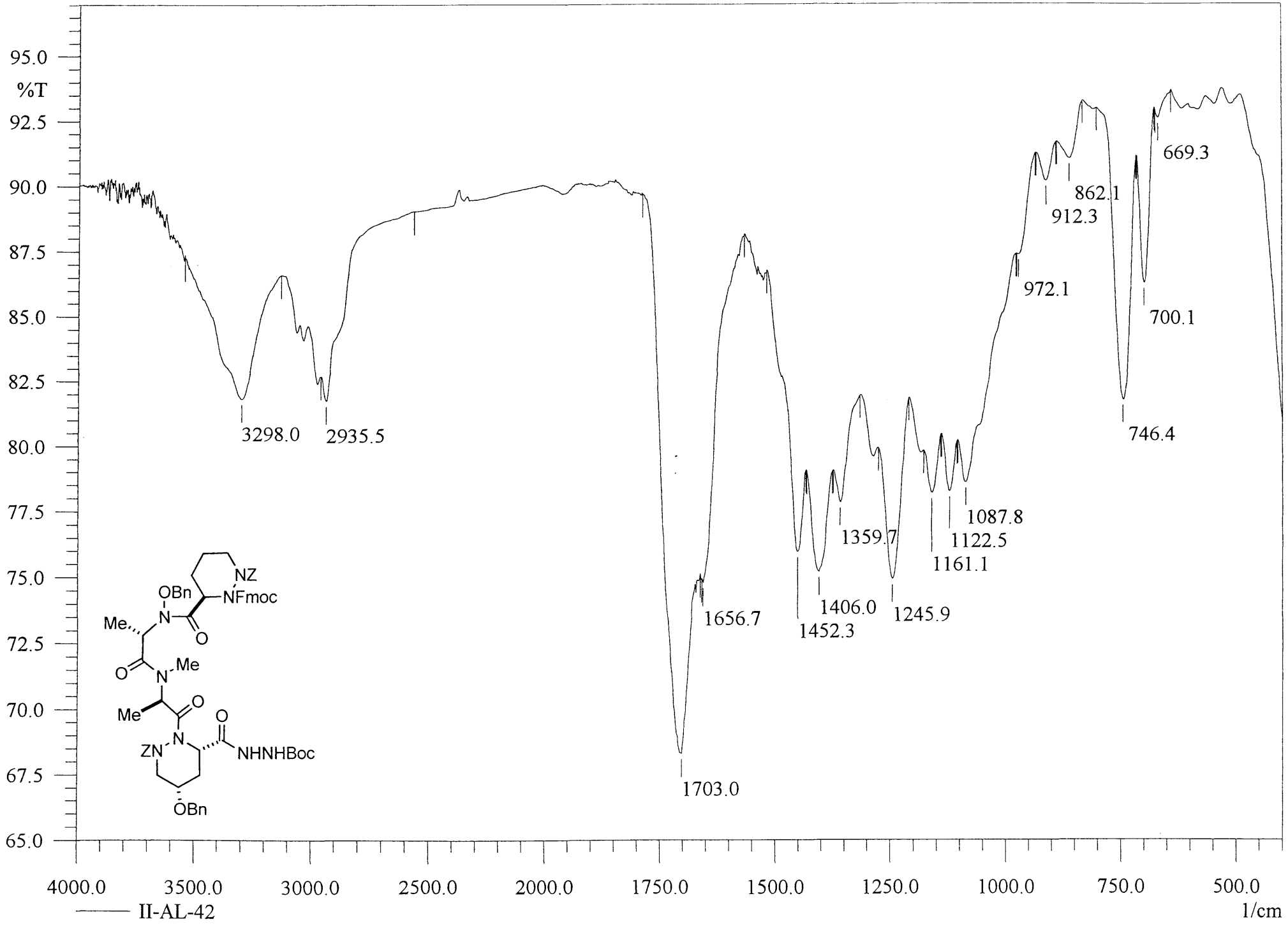


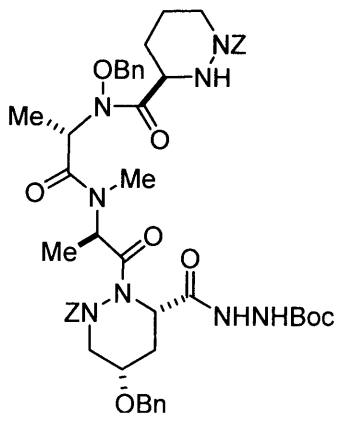
II-AL-42
HMQC
CDCl3 - 298K



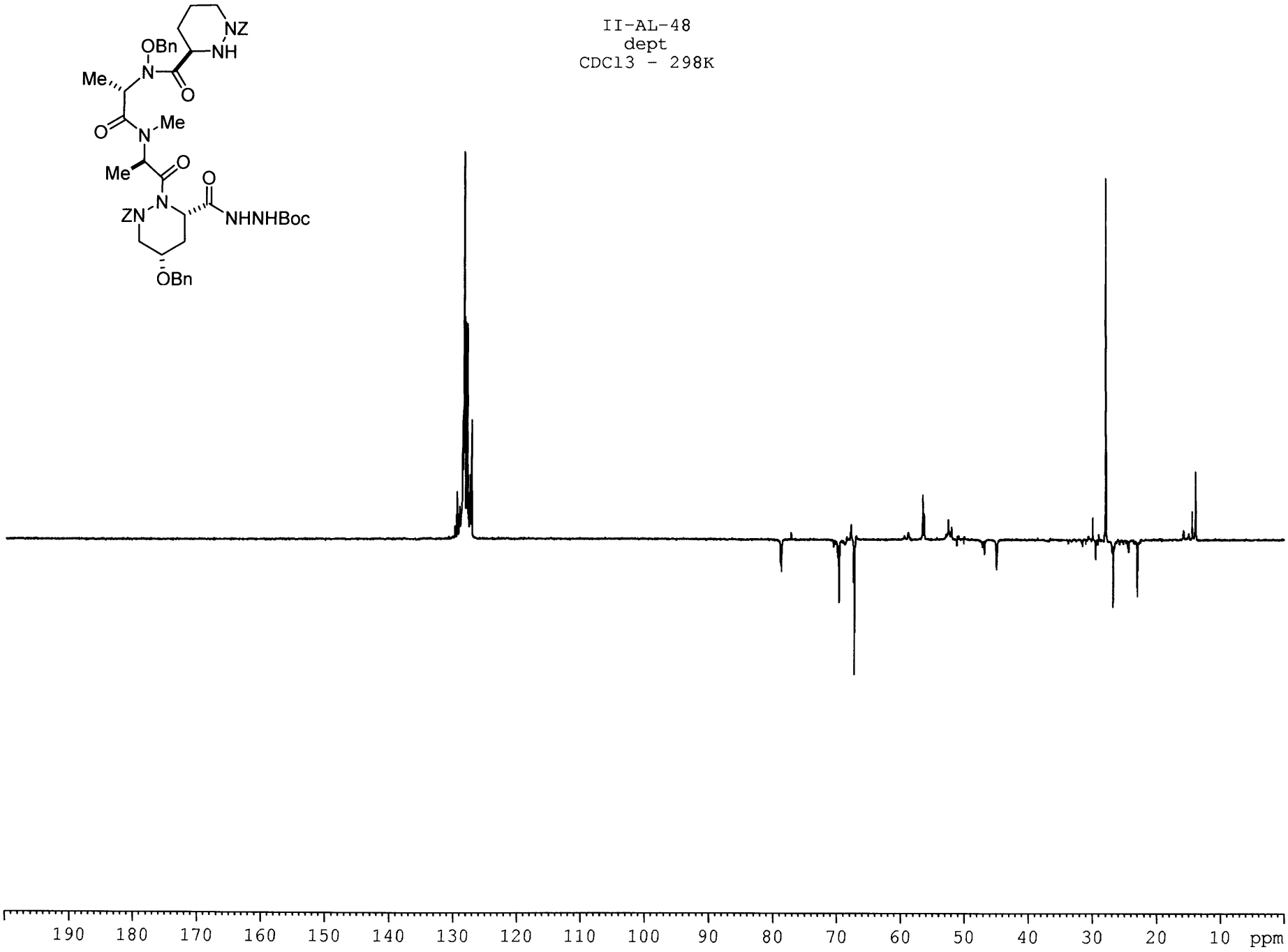


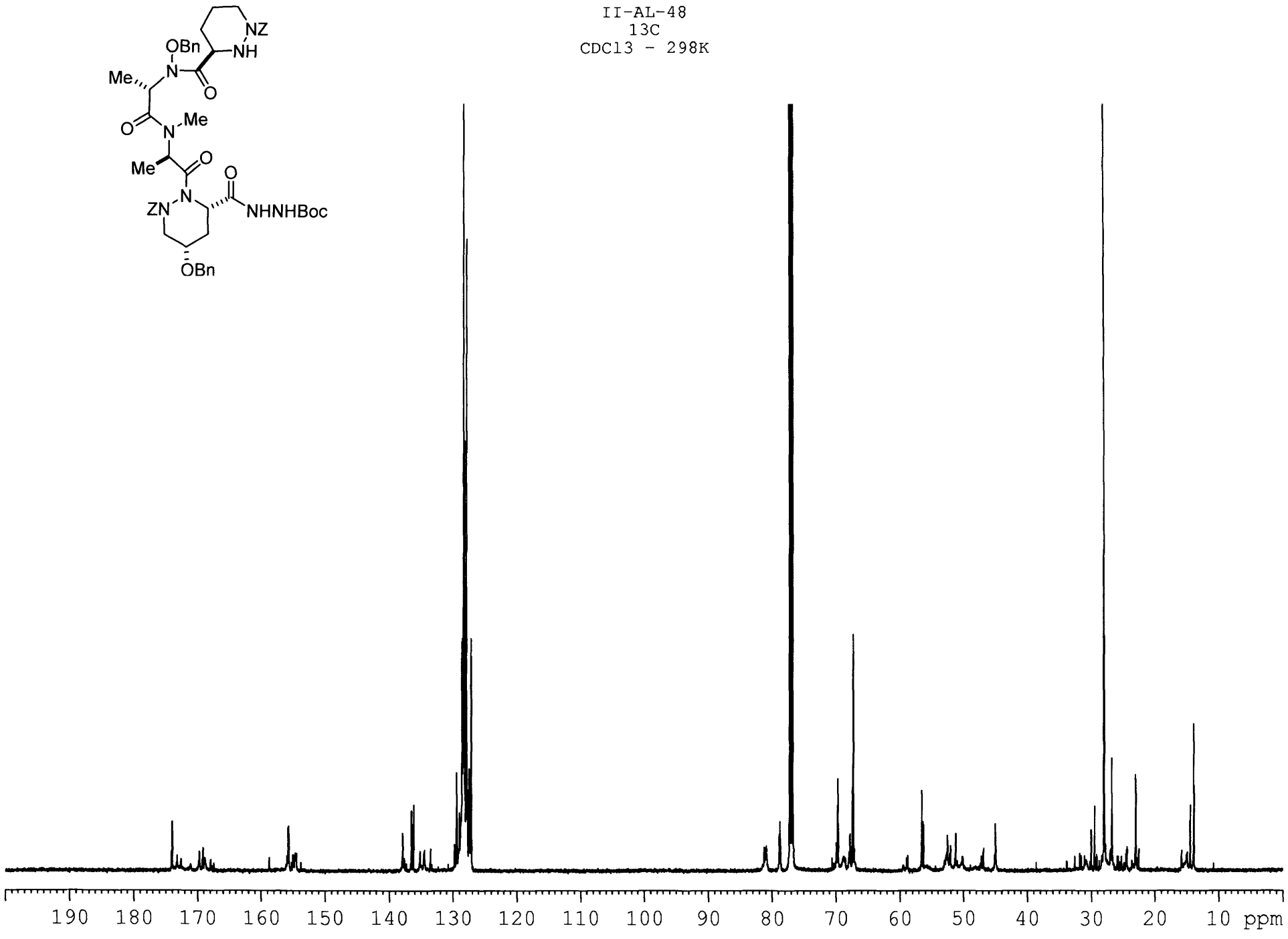

01131204: Scan Avg 142-143 (32.93 - 33.17 min) - Back
Base: 176.00 Int: 3.52667e+006 Sample: VG-70SE Positive Ion FAB
Sample: IIAL42
Instrument Resolution: 7000
Theoretical Mass: (M+Na) 1237.52219
Measured Mass: 1237.52395
Error: 1.42 ppm
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
176
326
413
245
629
1237
100
500
1000
1400
m/z
NZ
OBn
NFmoc
Me
N
O
O
N
Me
Me
O
O
N
ZN
NHNHBoc
OBn

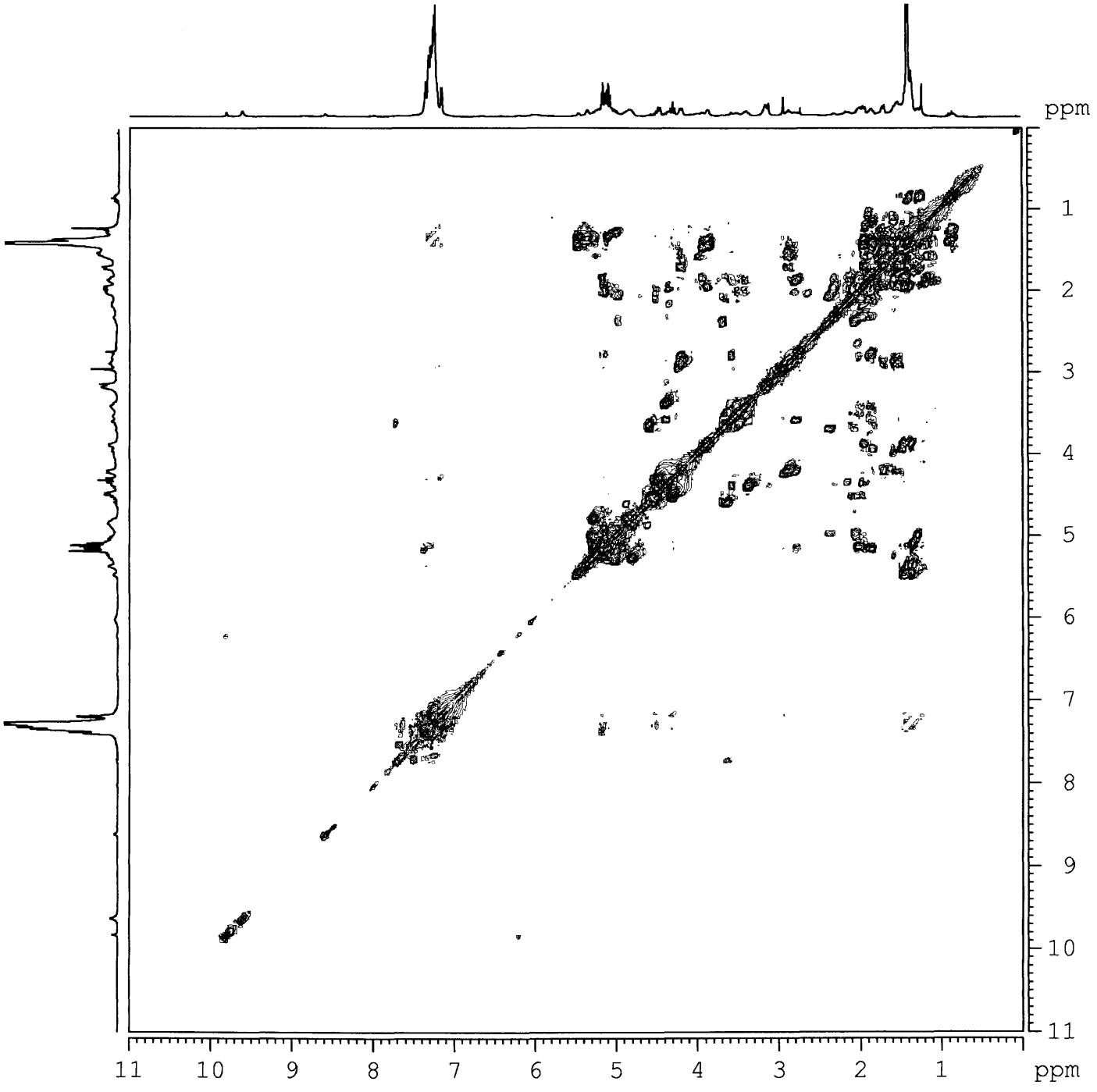

95.0
%T
92.5
90.0
87.5
85.0
82.5
80.0
77.5
75.0
72.5
70.0
67.5
65.0
3298.0
2935.5
1703.0
1656.7
1452.3
1406.0
1359.7
1245.9
1161.1
1122.5
1087.8
972.1
912.3
862.1
746.4
700.1
669.3
NZ
NFmoc
OBn
N
O
Me
N
Me
O
Me
O
N
ZN
O
NHNHBoc
OBn
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
II-AL-42



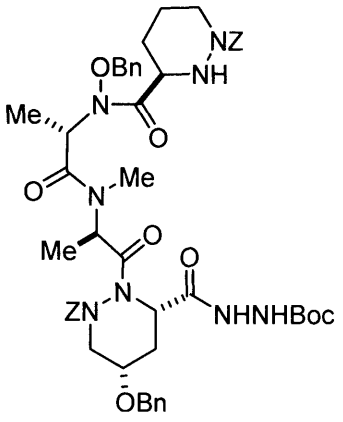
II-AL-48
CDCl3 - 298K

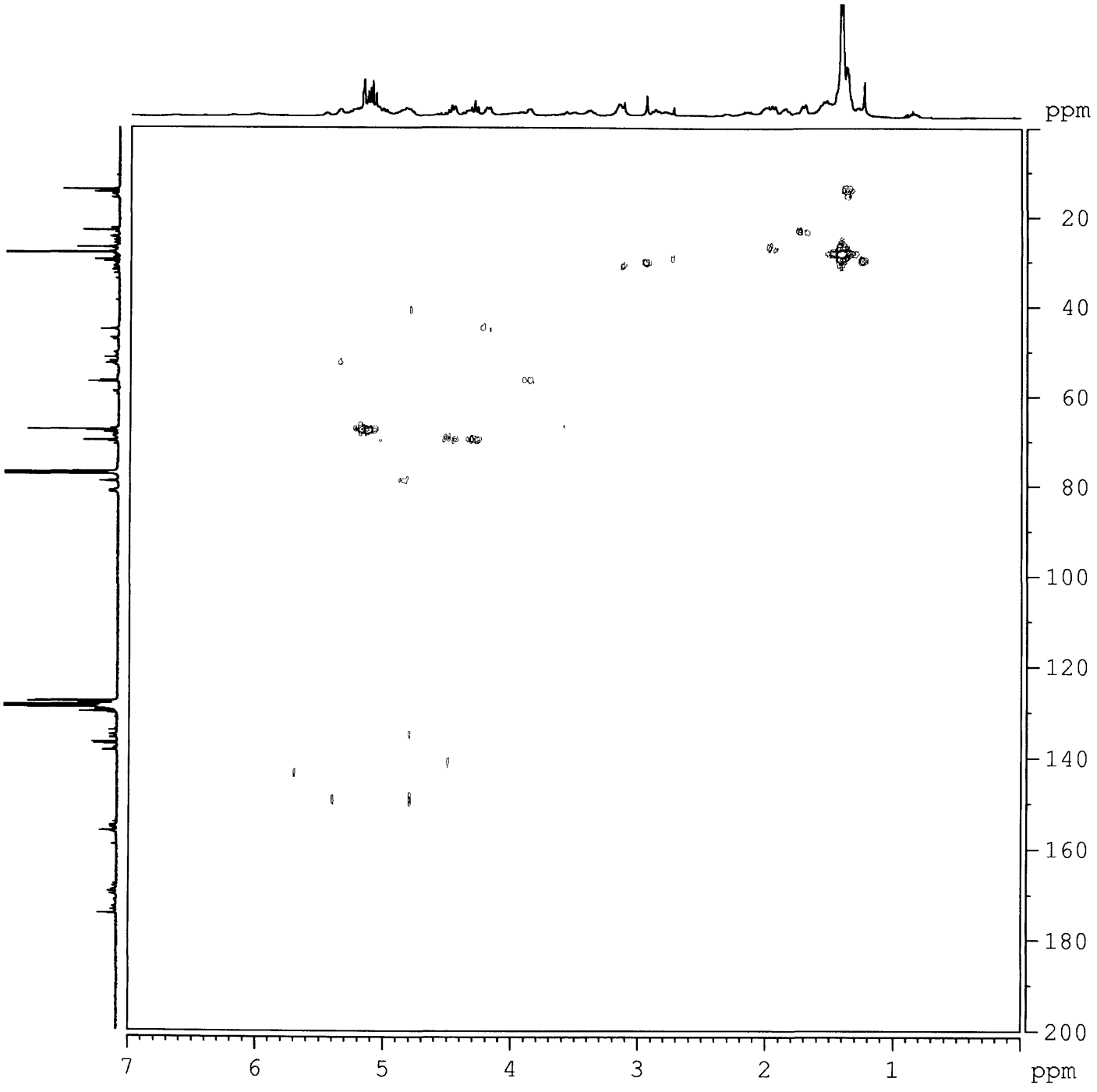

II-AL-48
dept
CDCl3 - 298K
NZ
NH
OBn
N
Me
O
N
Me
O
Me
O
O
N
ZN
NHNHBoc
OBn
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


II-AL-48
13C
CDCl3 - 298K
NZ
NH
OBn
N
Me
O
N
Me
O
Me
O
N
ZN
O
NHNHBoc
OBn
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

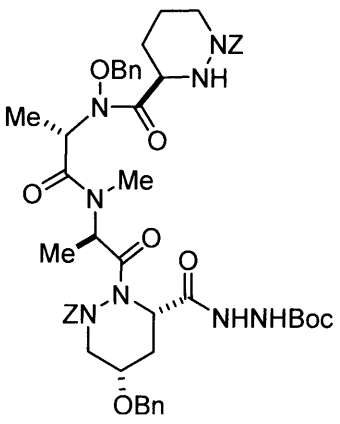


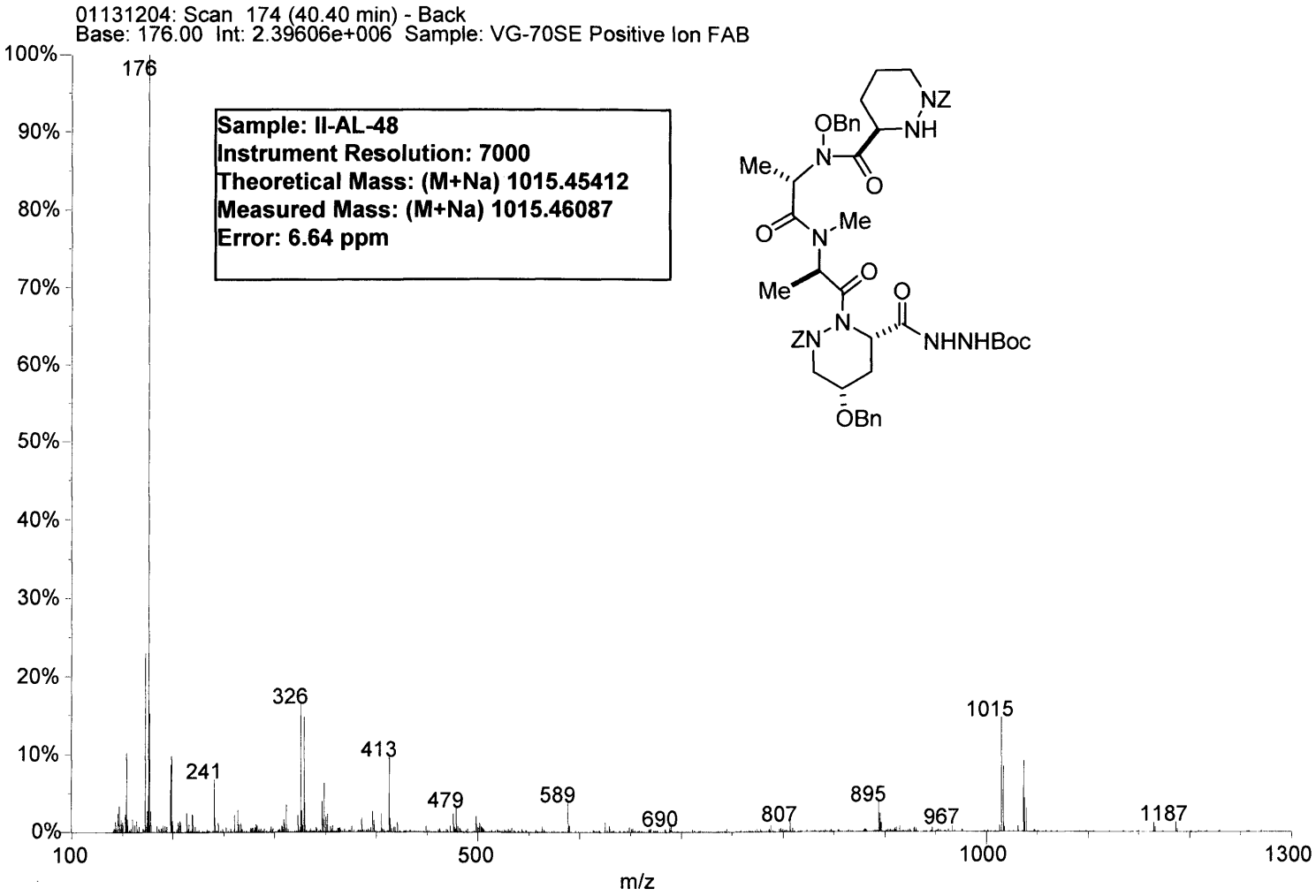
II-AL-48
cosy
CDCl3 - 298K

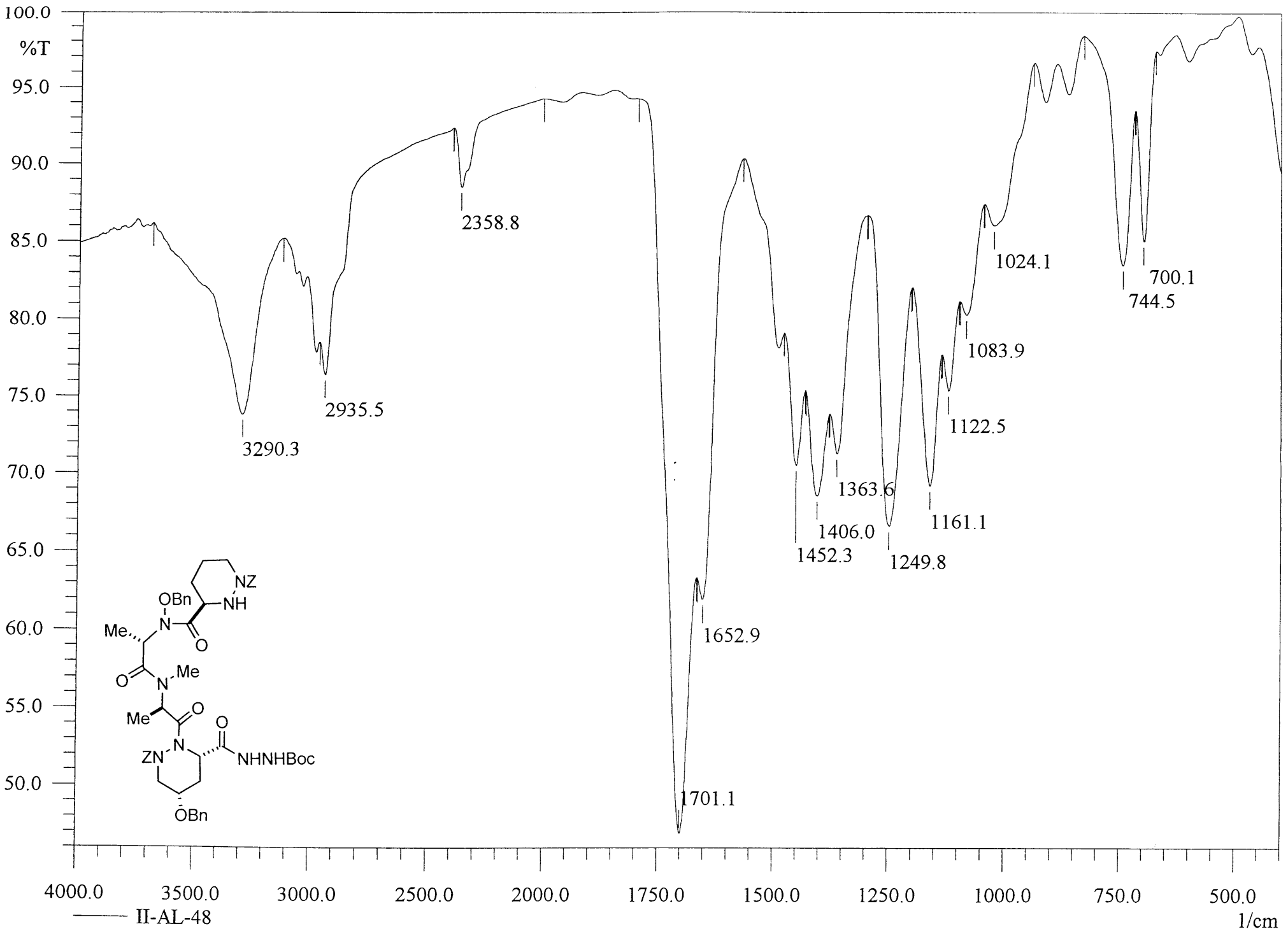




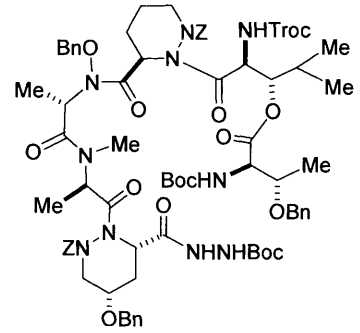
II-AL-48
HMQC
CDCl3 - 298K

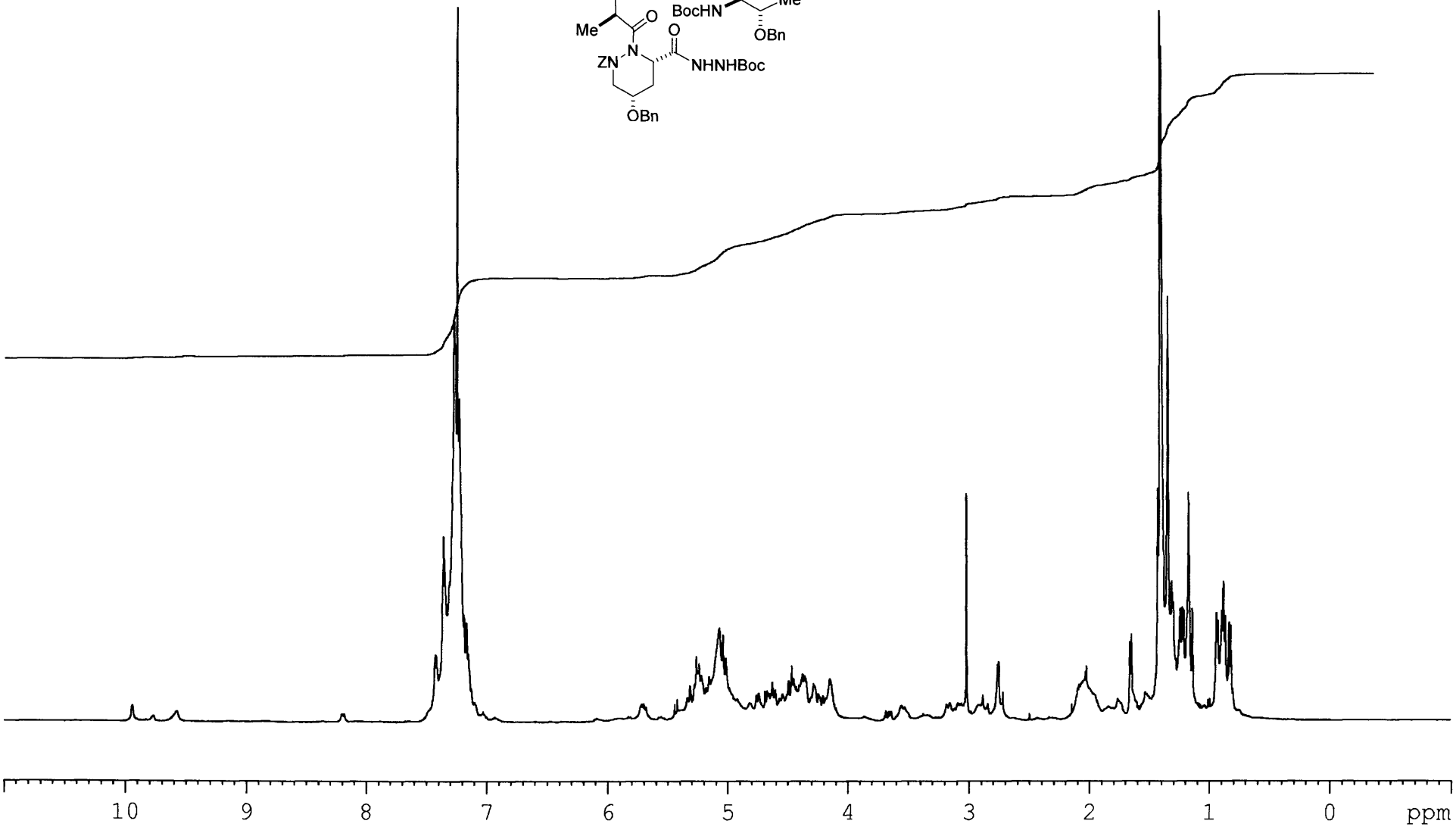



01131204: Scan 174 (40.40 min) - Back
Base: 176.00 Int: 2.39606e+006 Sample: VG-70SE Positive Ion FAB
Sample: II-AL-48
Instrument Resolution: 7000
Theoretical Mass: (M+Na) 1015.45412
Measured Mass: (M+Na) 1015.46087
Error: 6.64 ppm
NZ
OBn
NH
Me
N
O
O
N
Me
Me
O
O
N
ZN
NHNHBoc
OBn
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
176
326
241
413
479
589
690
807
895
967
1015
1187
100
500
1000
1300
m/z

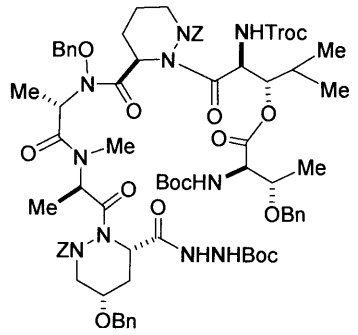

100.0
%T
95.0
90.0
85.0
80.0
75.0
70.0
65.0
60.0
55.0
50.0
3290.3
2935.5
2358.8
1701.1
1652.9
1452.3
1406.0
1363.6
1249.8
1161.1
1122.5
1083.9
1024.1
744.5
700.1
NZ
NH
OBn
N
O
Me
N
Me
O
Me
O
O
N
ZN
NHNHBoc
OBn
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
II-AL-48

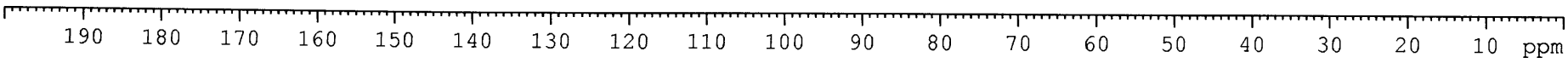
II-AL-110
CDCl3 - 298K



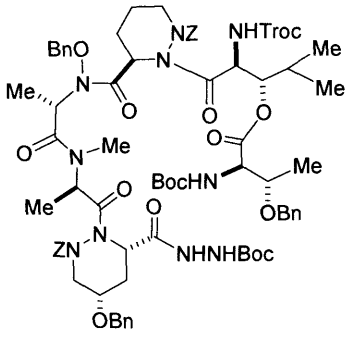


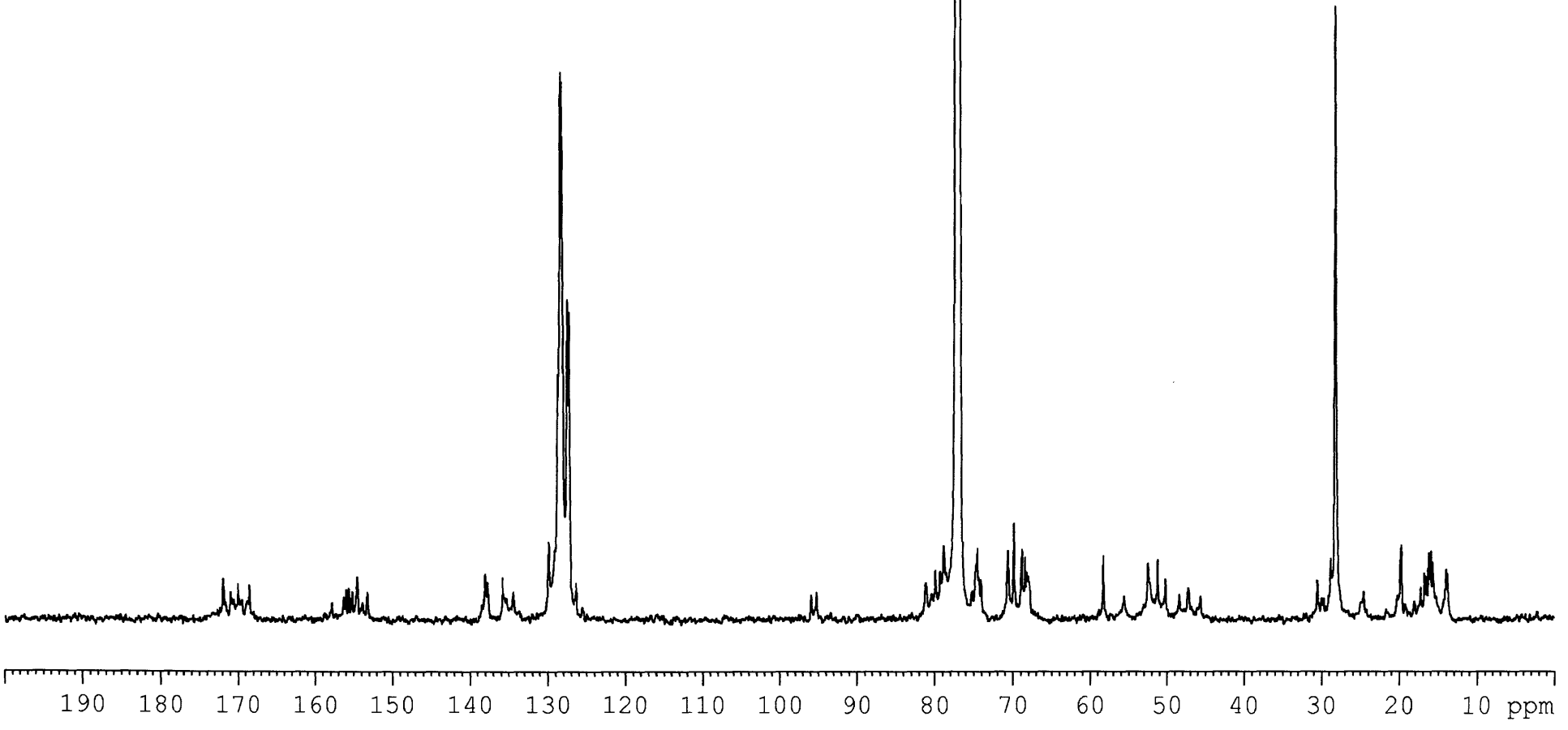
II-AL-110-1
DEPT
CDCl3 - 298K

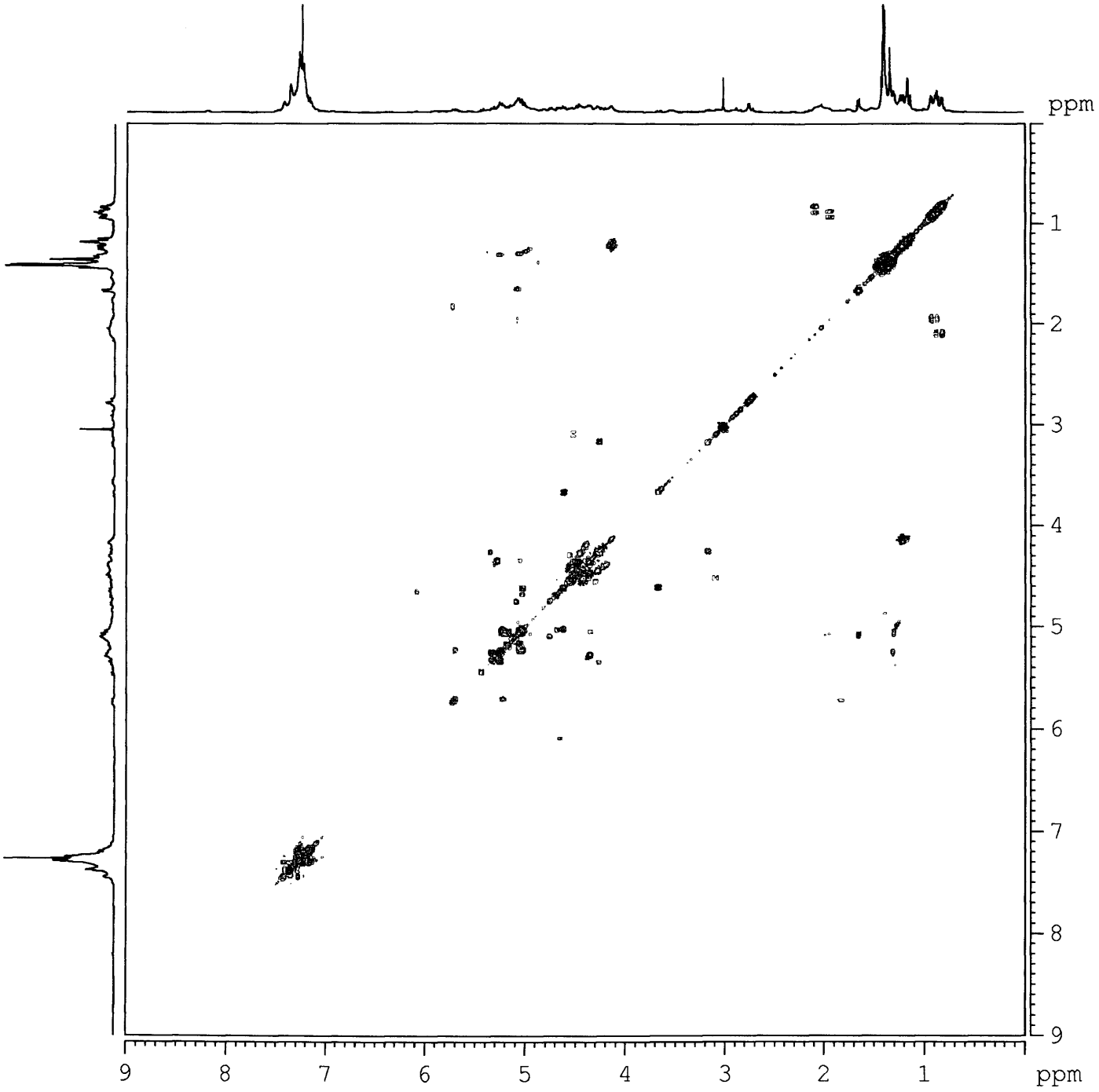




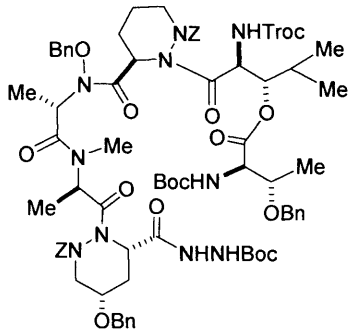
II-AL-110
13C
CDCl3 - 298K



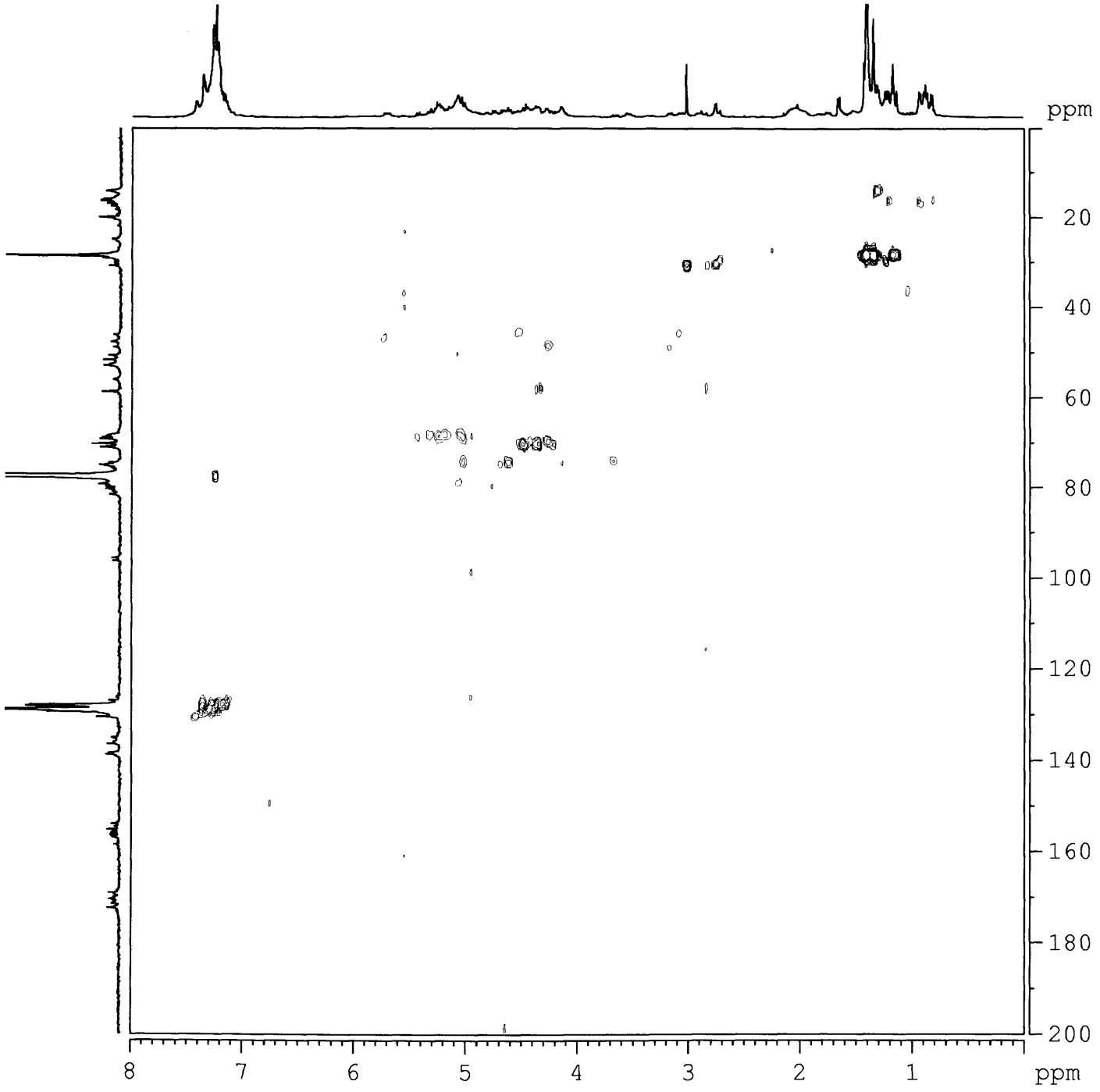


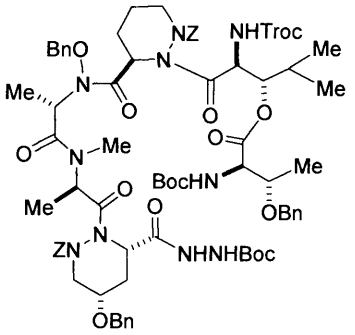


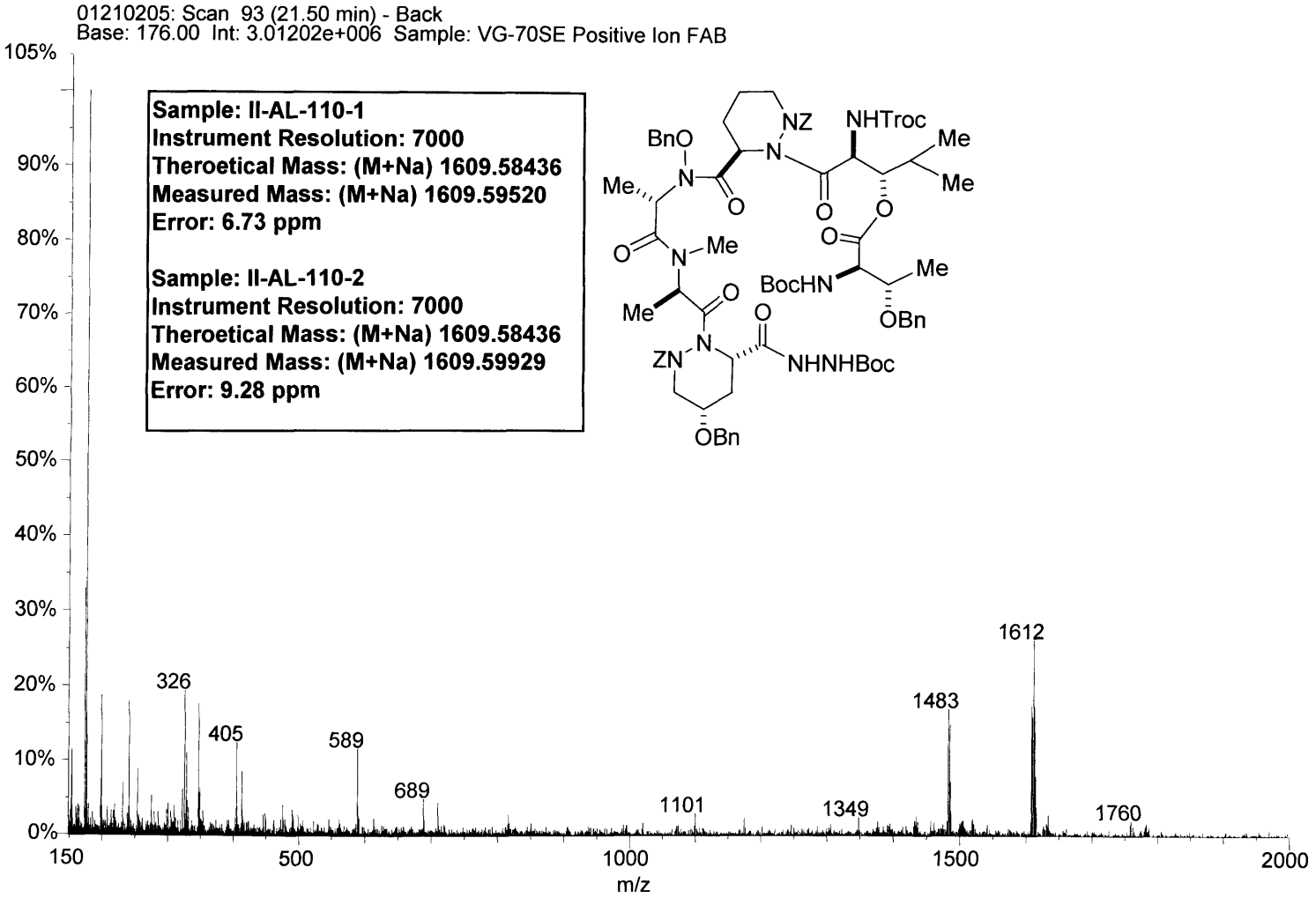
II-AL-110-1
COSY
CDCl3 - 298K



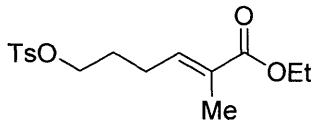
II-AL-110
HMQC
CDCl3 - 298K

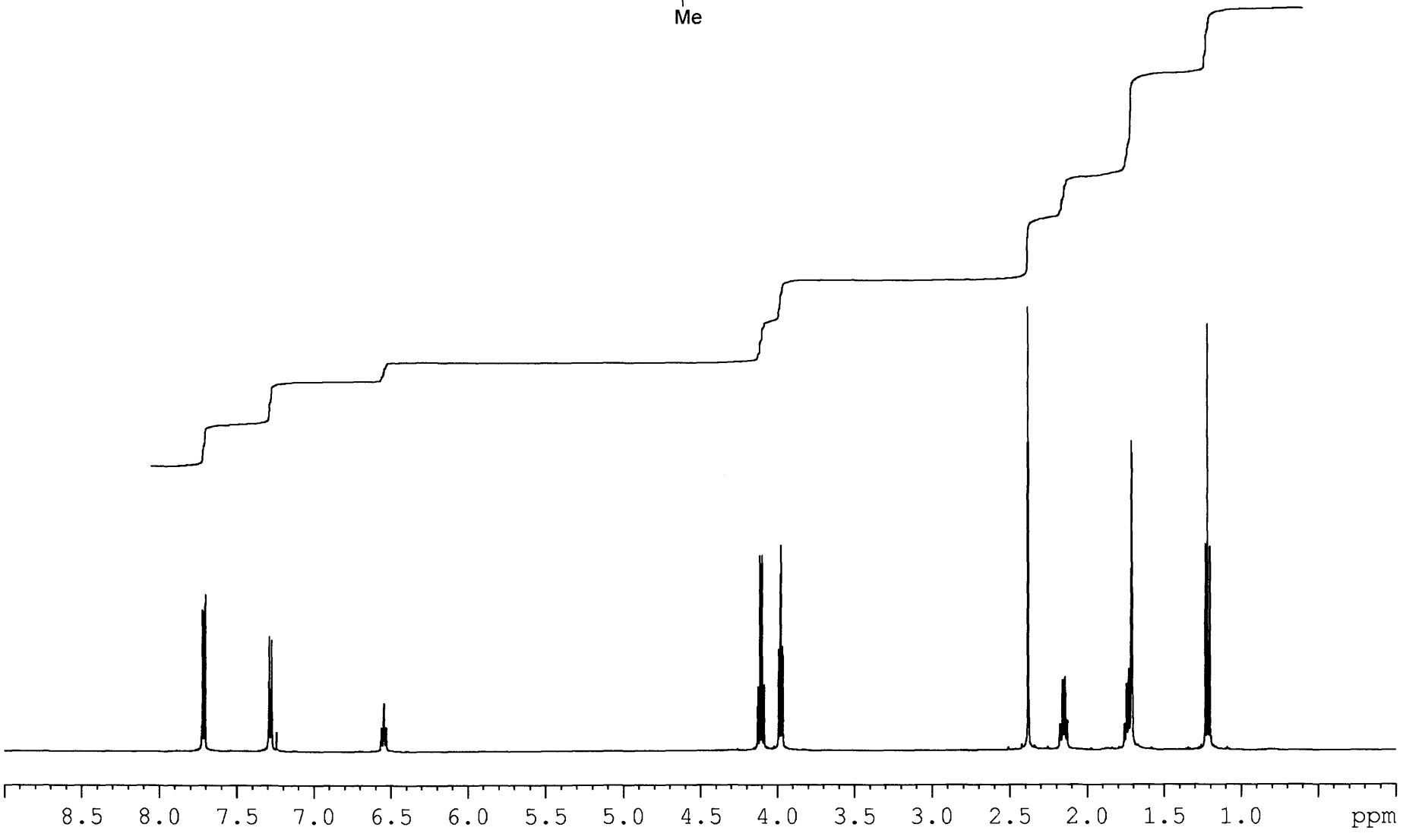




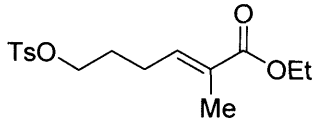

01210205: Scan 93 (21.50 min) - Back
Base: 176.00 Int: 3.01202e+006 Sample: VG-70SE Positive Ion FAB
Sample: II-AL-110-1
Instrument Resolution: 7000
Theroetical Mass: (M+Na) 1609.58436
Measured Mass: (M+Na) 1609.59520
Error: 6.73 ppm
Sample: II-AL-110-2
Instrument Resolution: 7000
Theroetical Mass: (M+Na) 1609.58436
Measured Mass: (M+Na) 1609.59929
Error: 9.28 ppm
BnO
NZ
NHTroc
Me
Me
Me
N
N
O
O
O
O
O
N
Me
O
BocHN
Me
Me
O
OBn
N
ZN
O
NHNHBoc
OBn
105%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
326
405
589
689
1101
1349
1483
1612
1760
150
500
1000
1500
2000
m/z

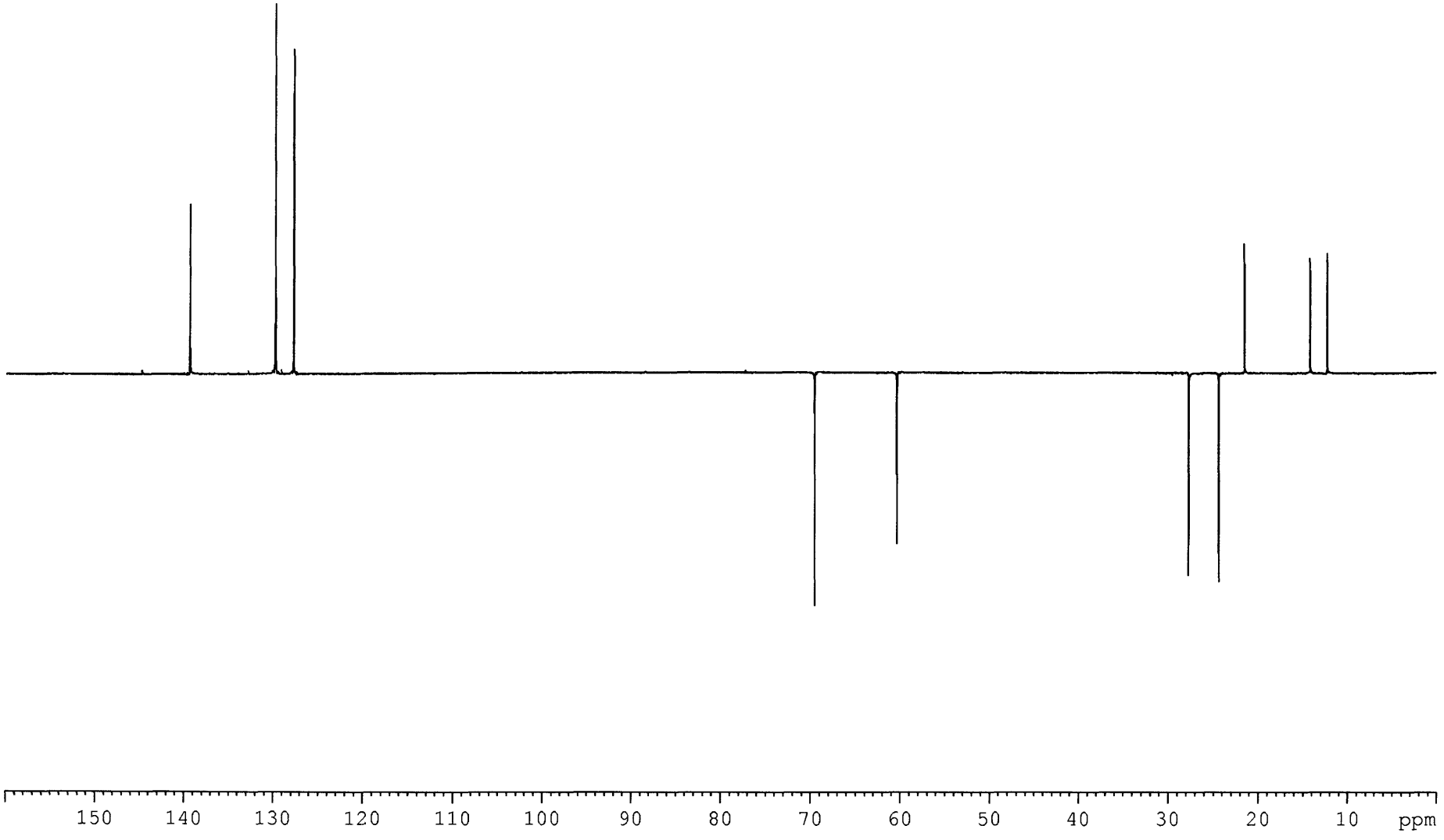
III-AL-15
CDCl3 - 298K



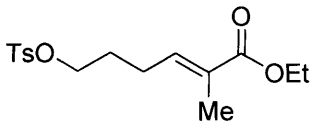


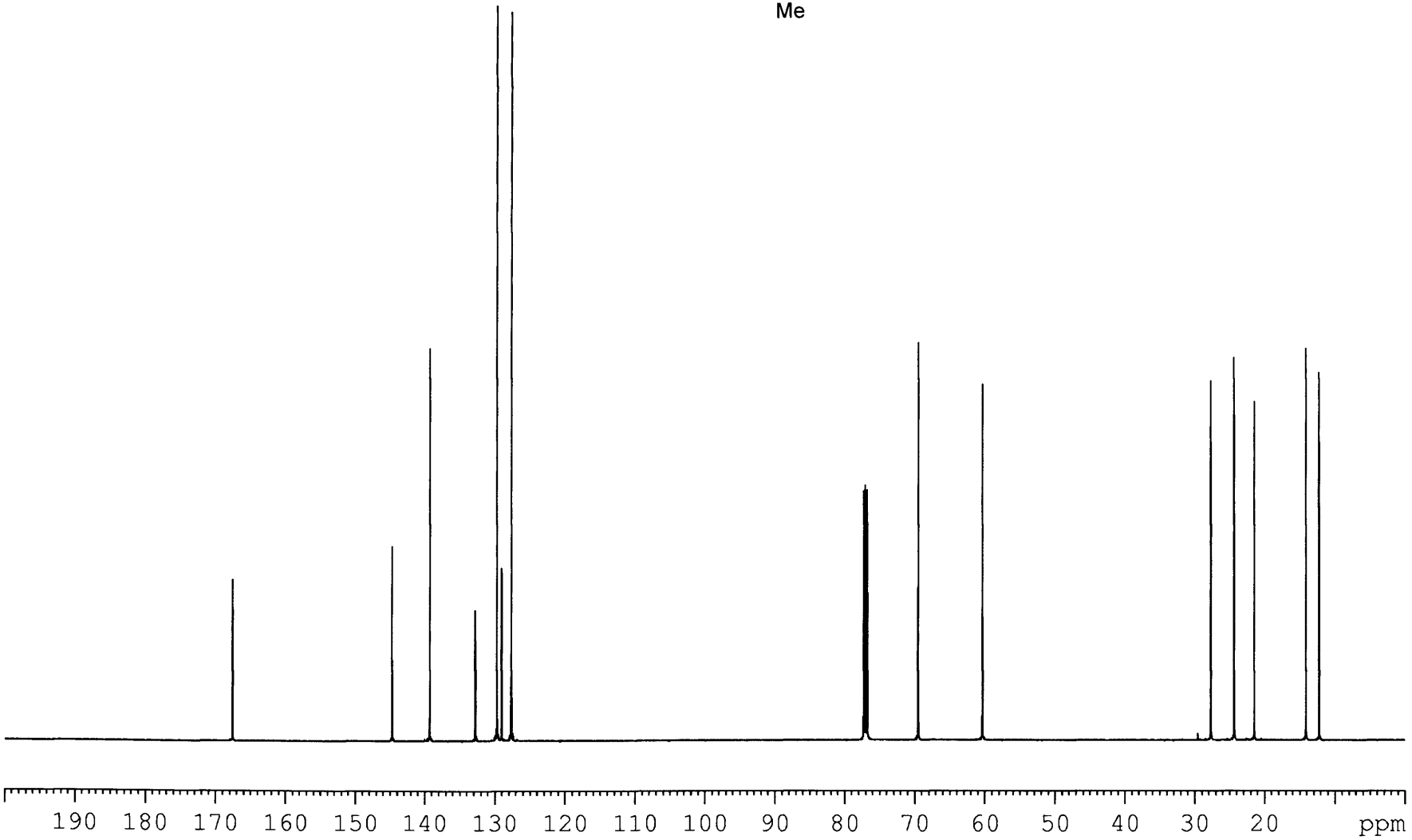
III-AL-15
dept
CDCl3 - 298K

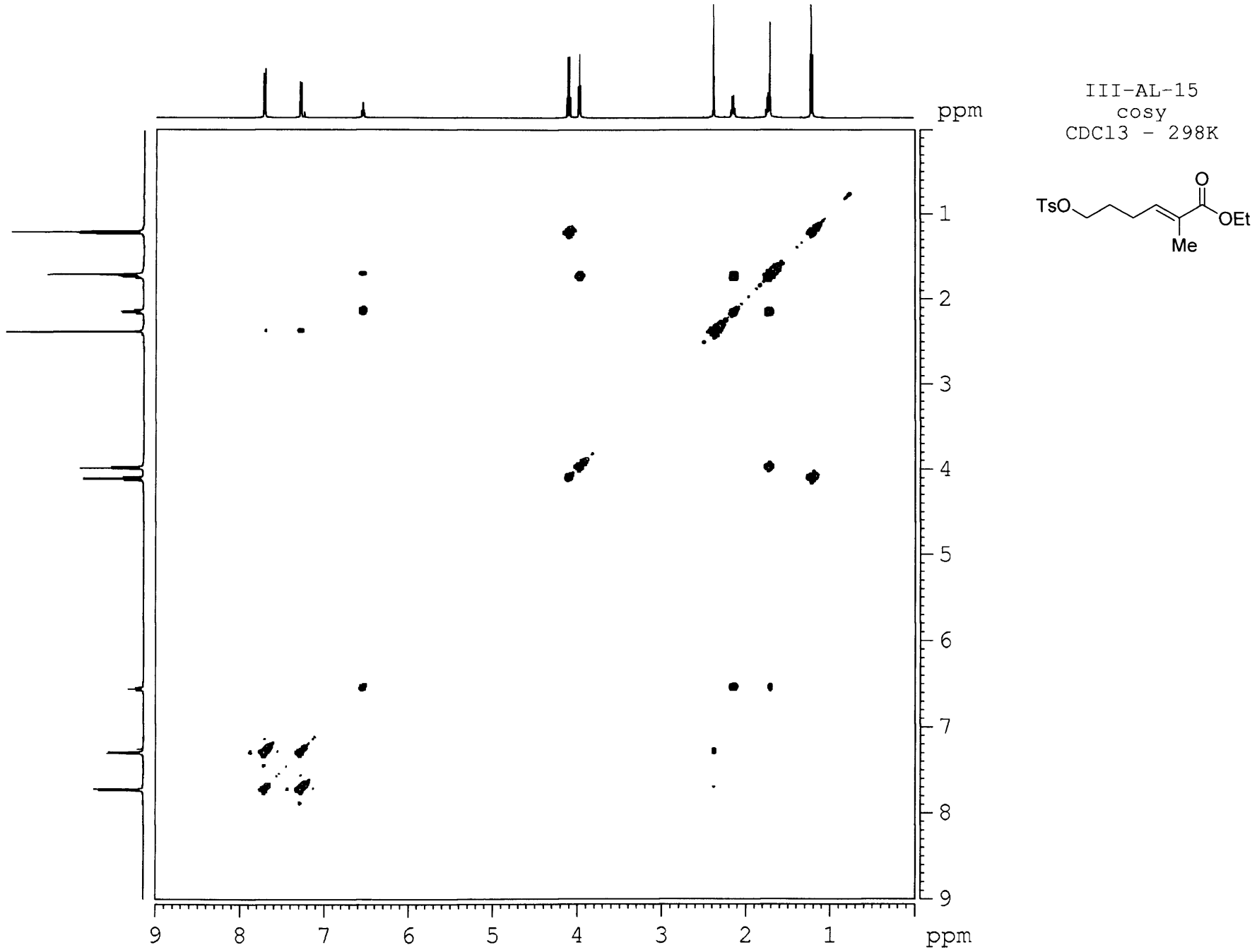




III-AL-15
13C
CDCl3 - 298K

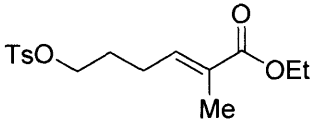


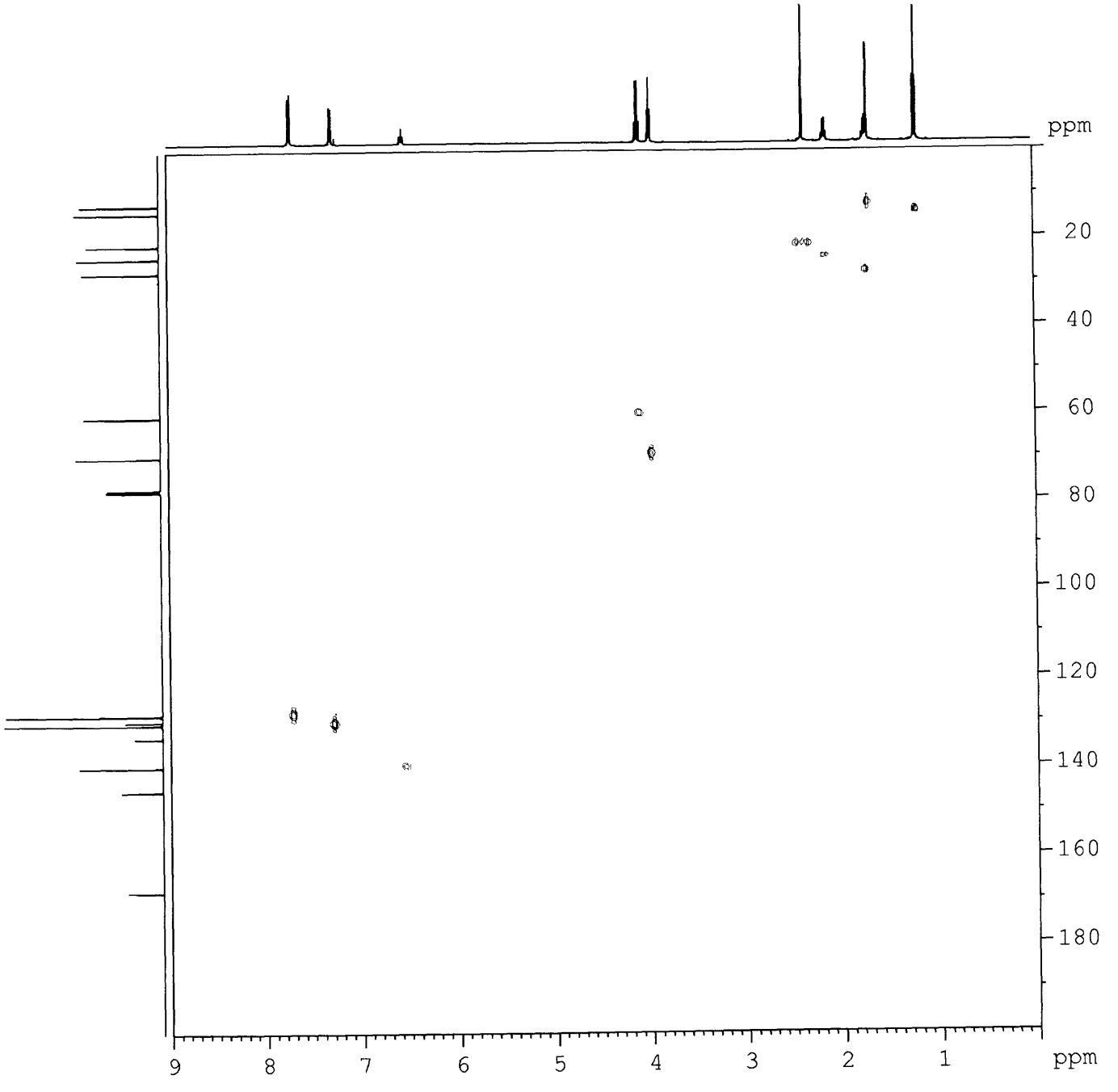




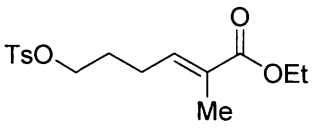
III-AL-15
cosy
CDCl3 - 298K

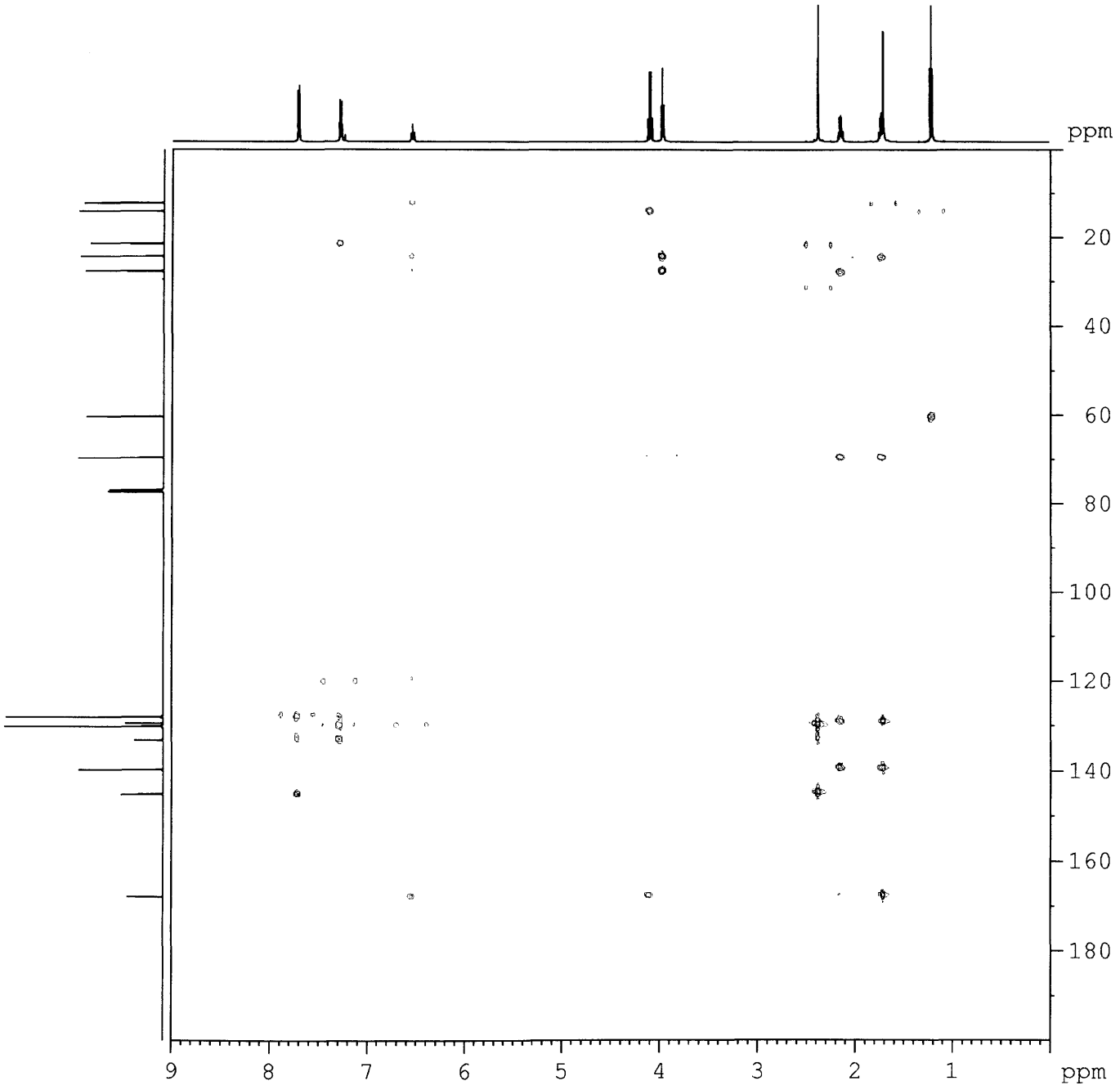
III-AL-15
HMQC
CDC13 - 298K

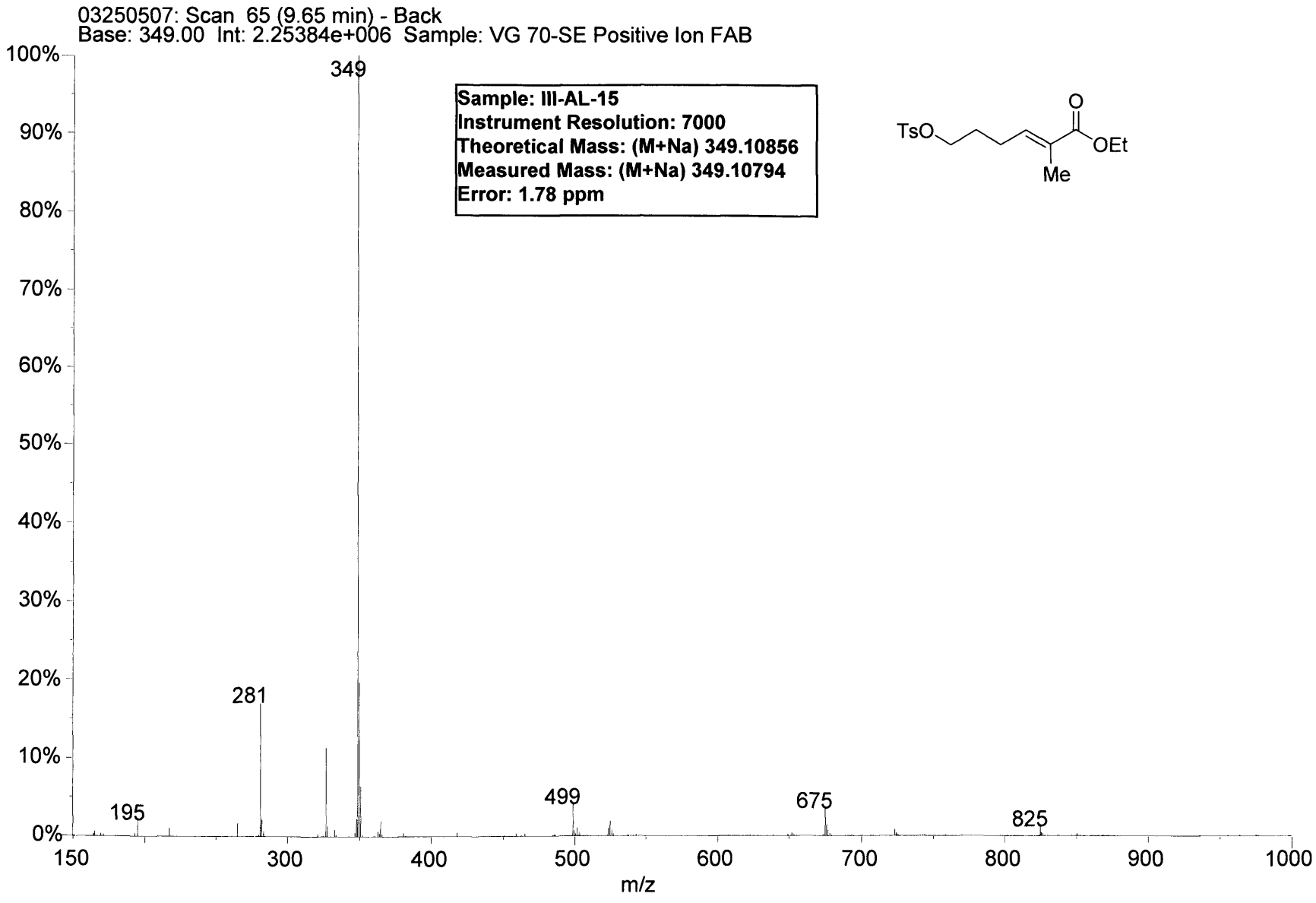


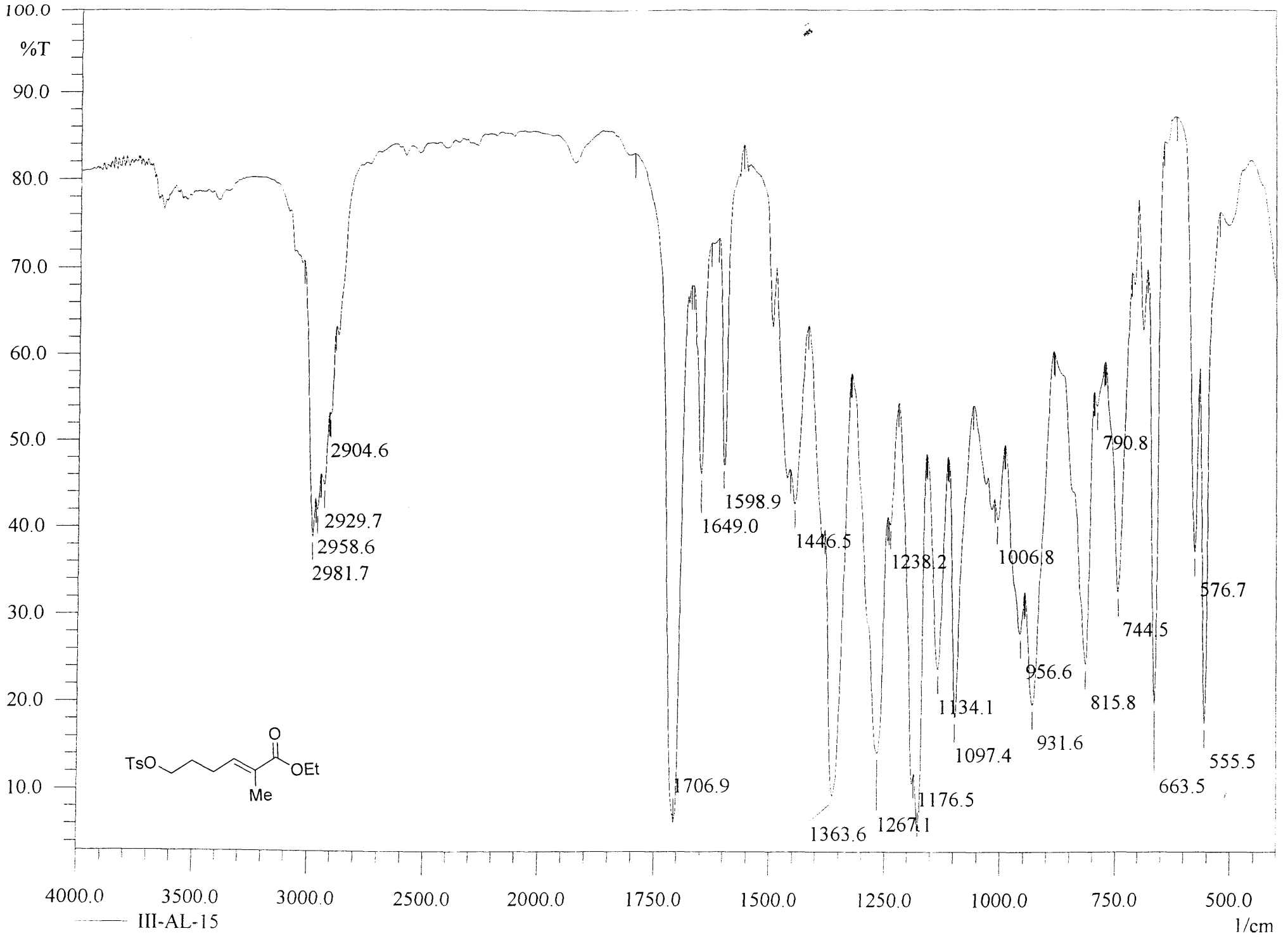


III-AL-15
HMBC
CDCl3 - 298K

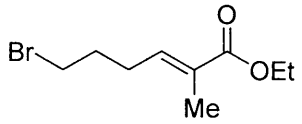


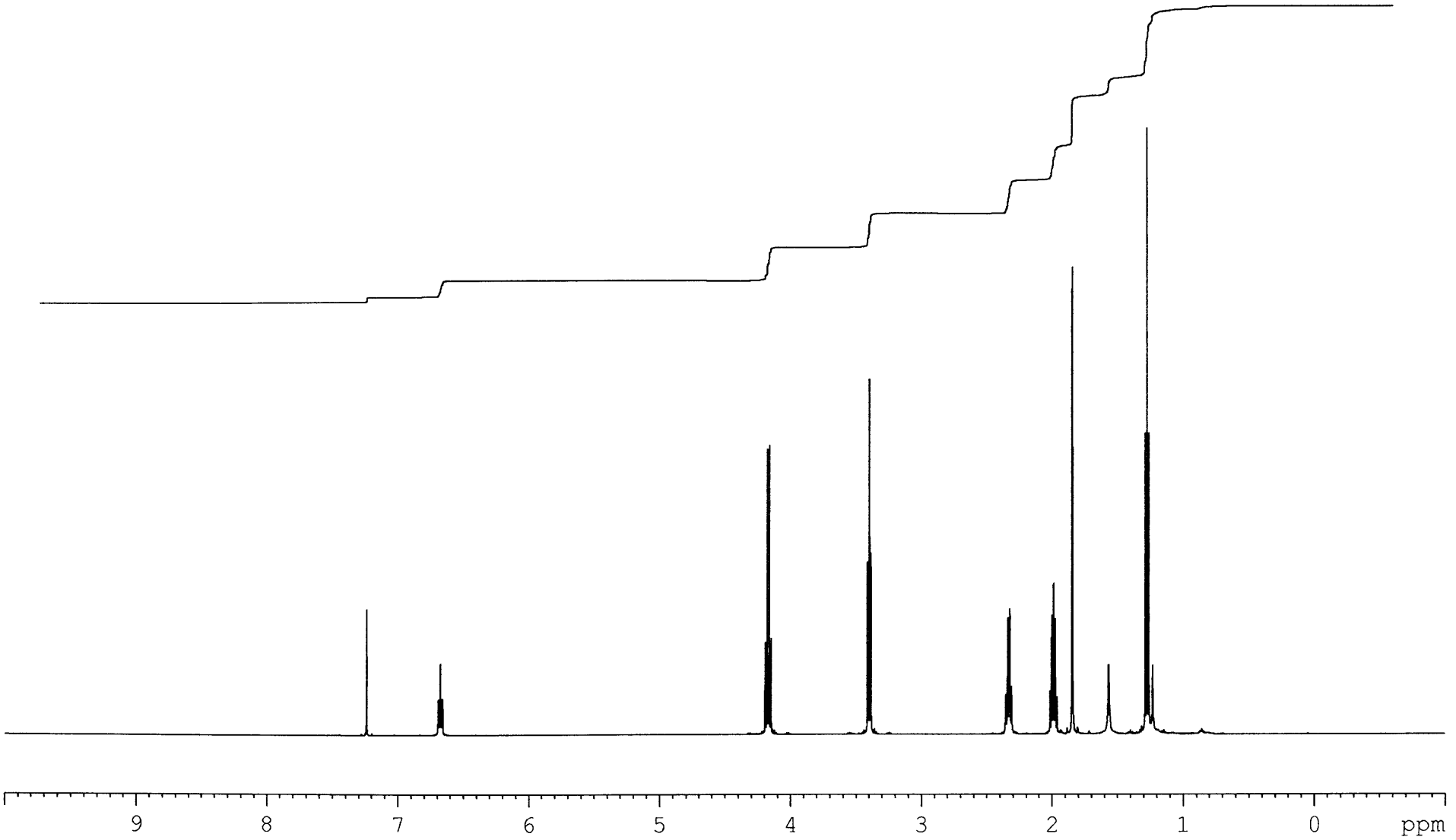



03250507: Scan 65 (9.65 min) - Back
Base: 349.00 Int: 2.25384e+006 Sample: VG 70-SE Positive Ion FAB
Sample: III-AL-15
Instrument Resolution: 7000
Theoretical Mass: (M+Na) 349.10856
Measured Mass: (M+Na) 349.10794
Error: 1.78 ppm
TsO
O
OEt
Me
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
349
281
195
499
675
825
150
300
400
500
600
700
800
900
1000
m/z

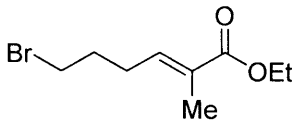

100.0
%T
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
2904.6
2929.7
2958.6
2981.7
1649.0
1598.9
1446.5
1706.9
1363.6
1267.1
1238.2
1176.5
1134.1
1097.4
1006.8
956.6
931.6
815.8
790.8
744.5
663.5
576.7
555.5
TsO
O
OEt
Me
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
III-AL-15

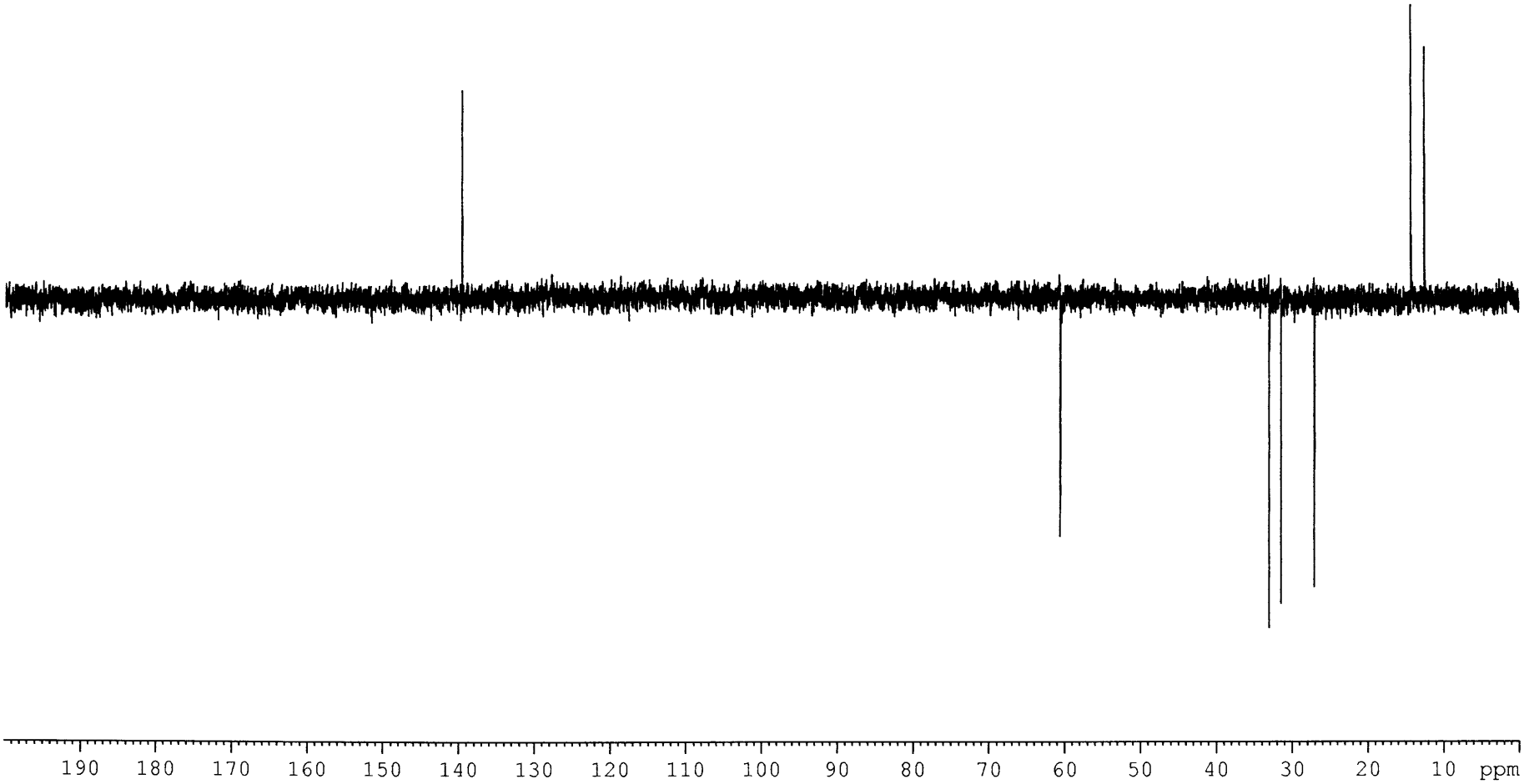
III-AL-68
CDCl3 - 298K



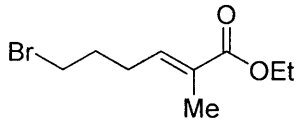


III-AL-68
DEPT
CDCl3 - 298K

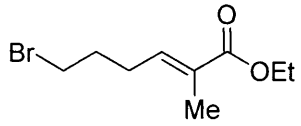


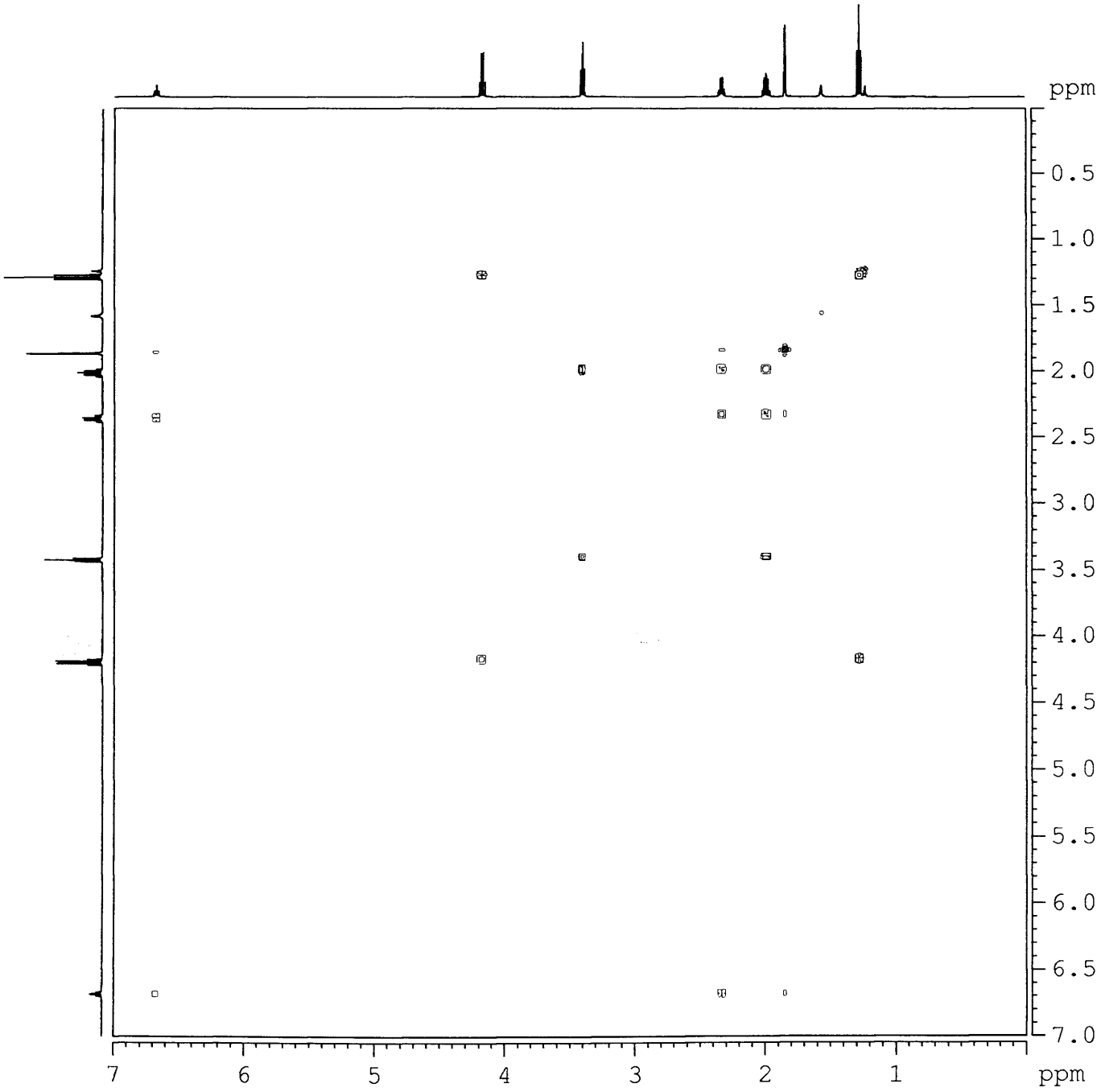


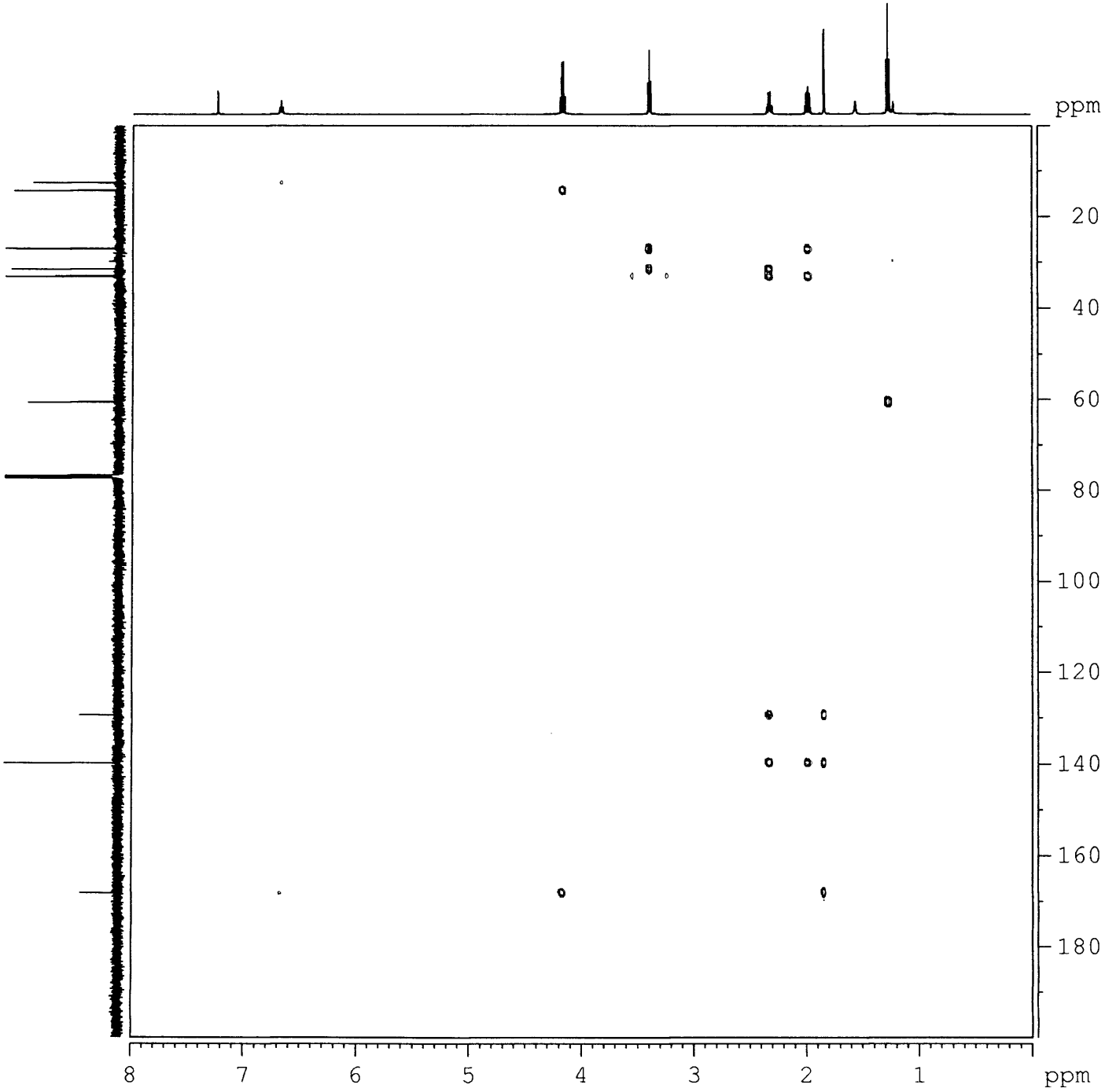
III-AL-68
13C
CDCl3 - 298K



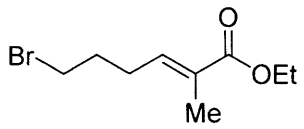
III-AL-68
COSY
CDCl3 - 298K

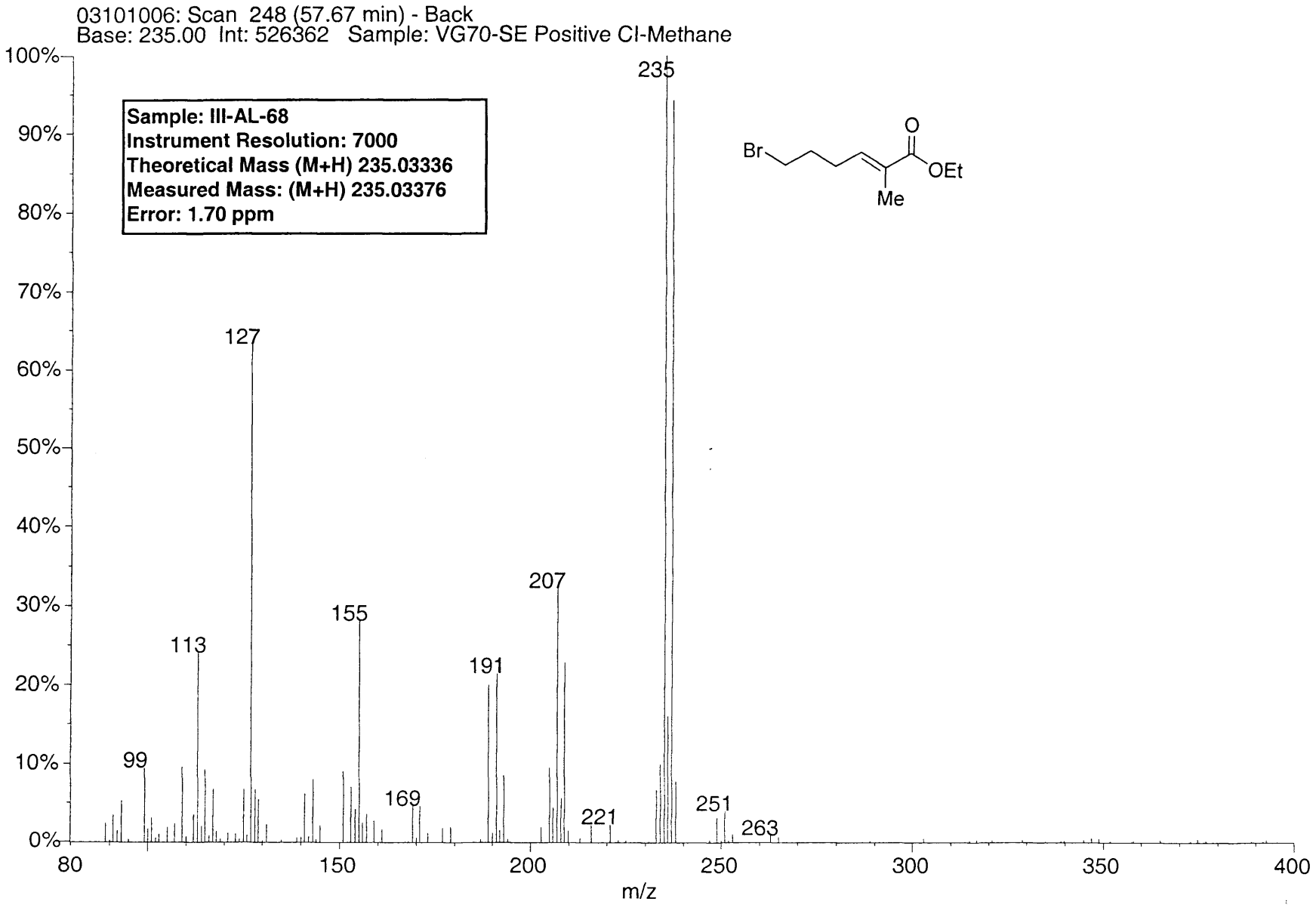


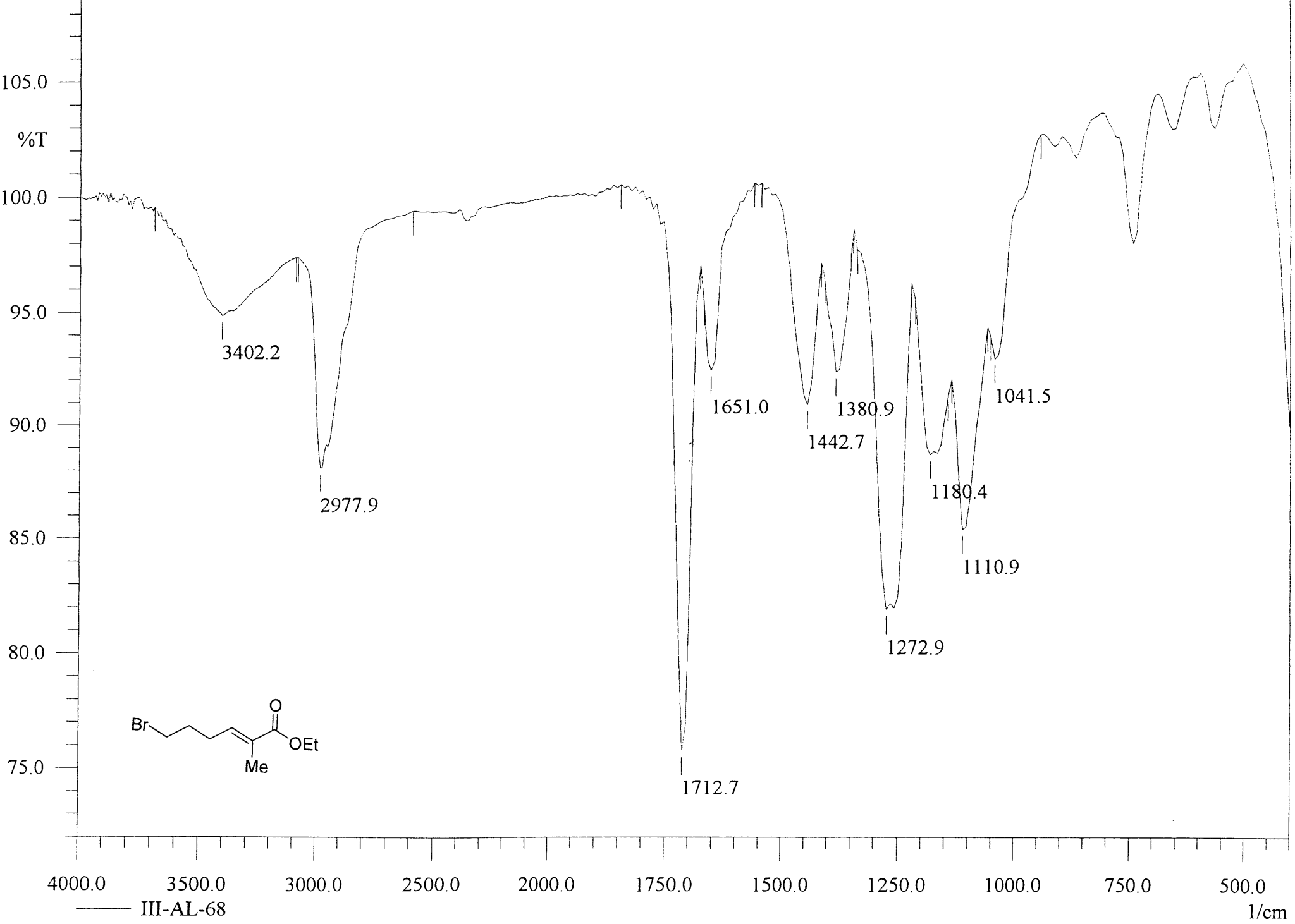




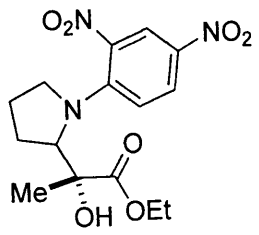
III-AL-68
HMBC
CDCl3 - 298K



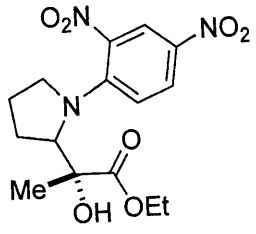

03101006: Scan 248 (57.67 min) - Back
Base: 235.00 Int: 526362 Sample: VG70-SE Positive CI-Methane
Sample: III-AL-68
Instrument Resolution: 7000
Theoretical Mass (M+H) 235.03336
Measured Mass: (M+H) 235.03376
Error: 1.70 ppm
Br
O
OEt
Me
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
235
127
207
155
113
191
99
169
221
251
263
80
150
200
250
300
350
400
m/z


105.0
%T
100.0
95.0
90.0
85.0
80.0
75.0
3402.2
2977.9
1712.7
1651.0
1442.7
1380.9
1272.9
1180.4
1110.9
1041.5
Br
O
OEt
Me
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
III-AL-68

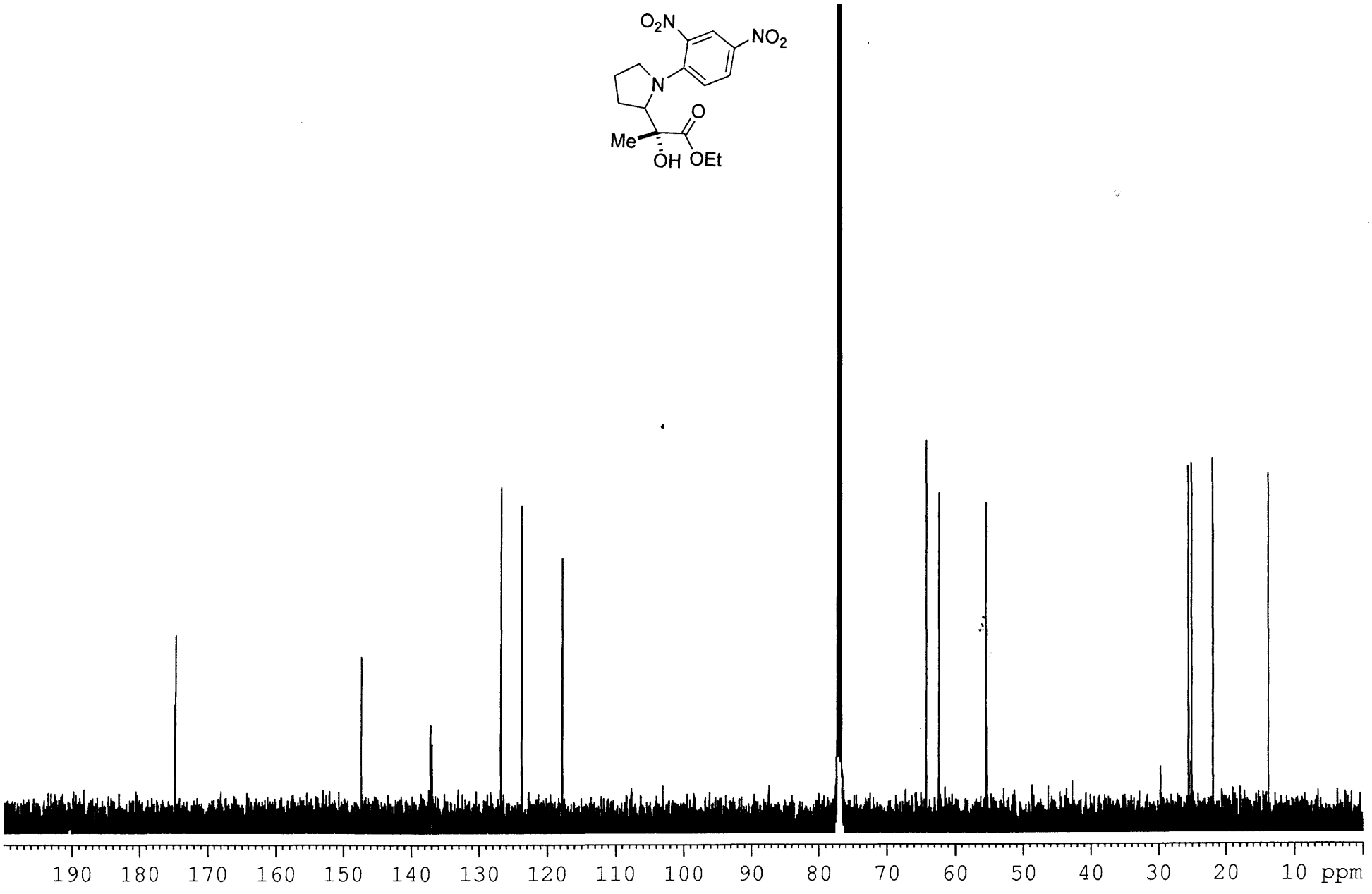
III-AL-63-3
CDCl3 - 298K



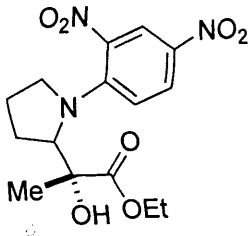
III-AL-63-3
DEPT
CDCl3 - 298K

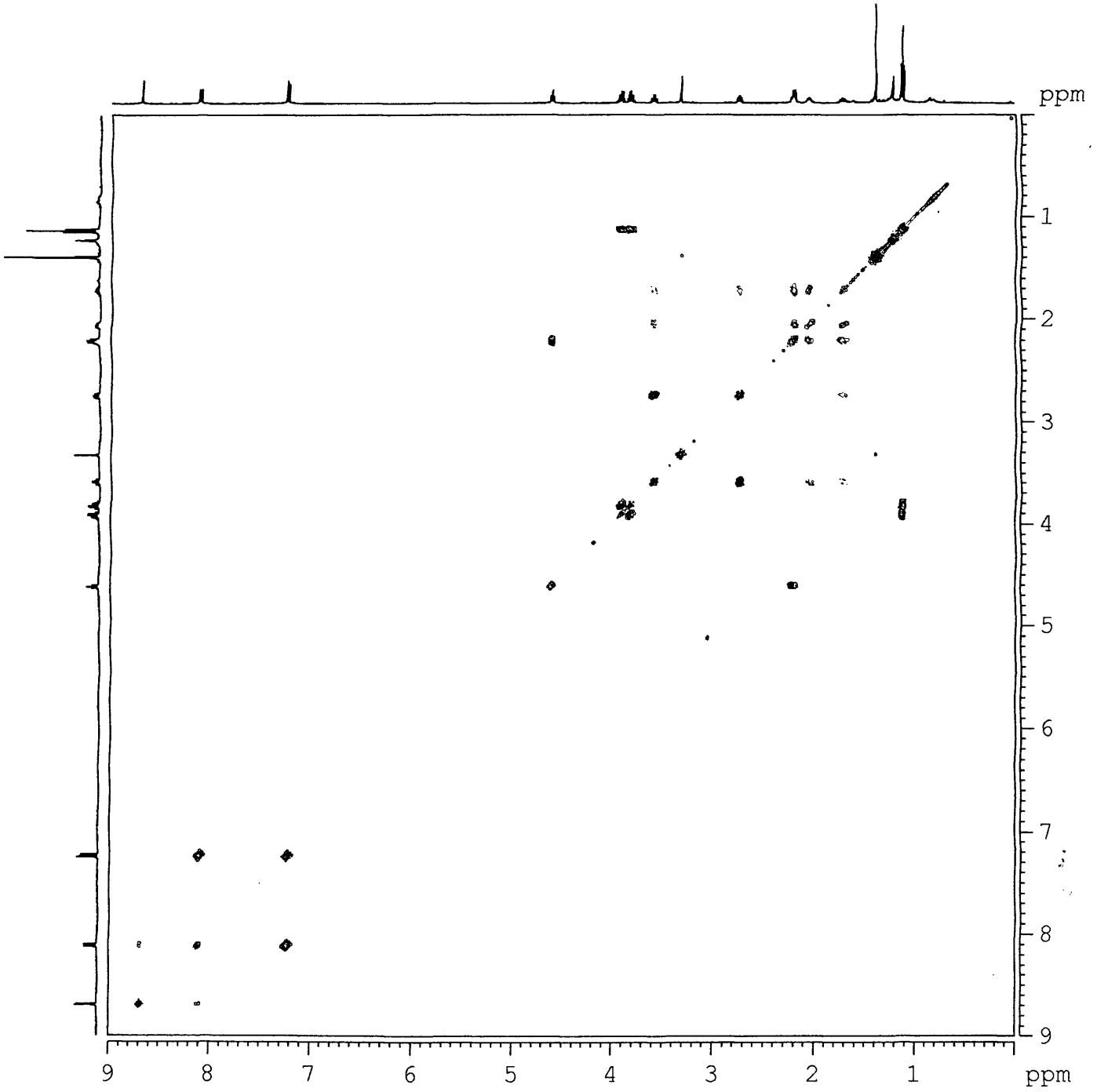


III-AL-63-3
13C
CDCl3 - 298K

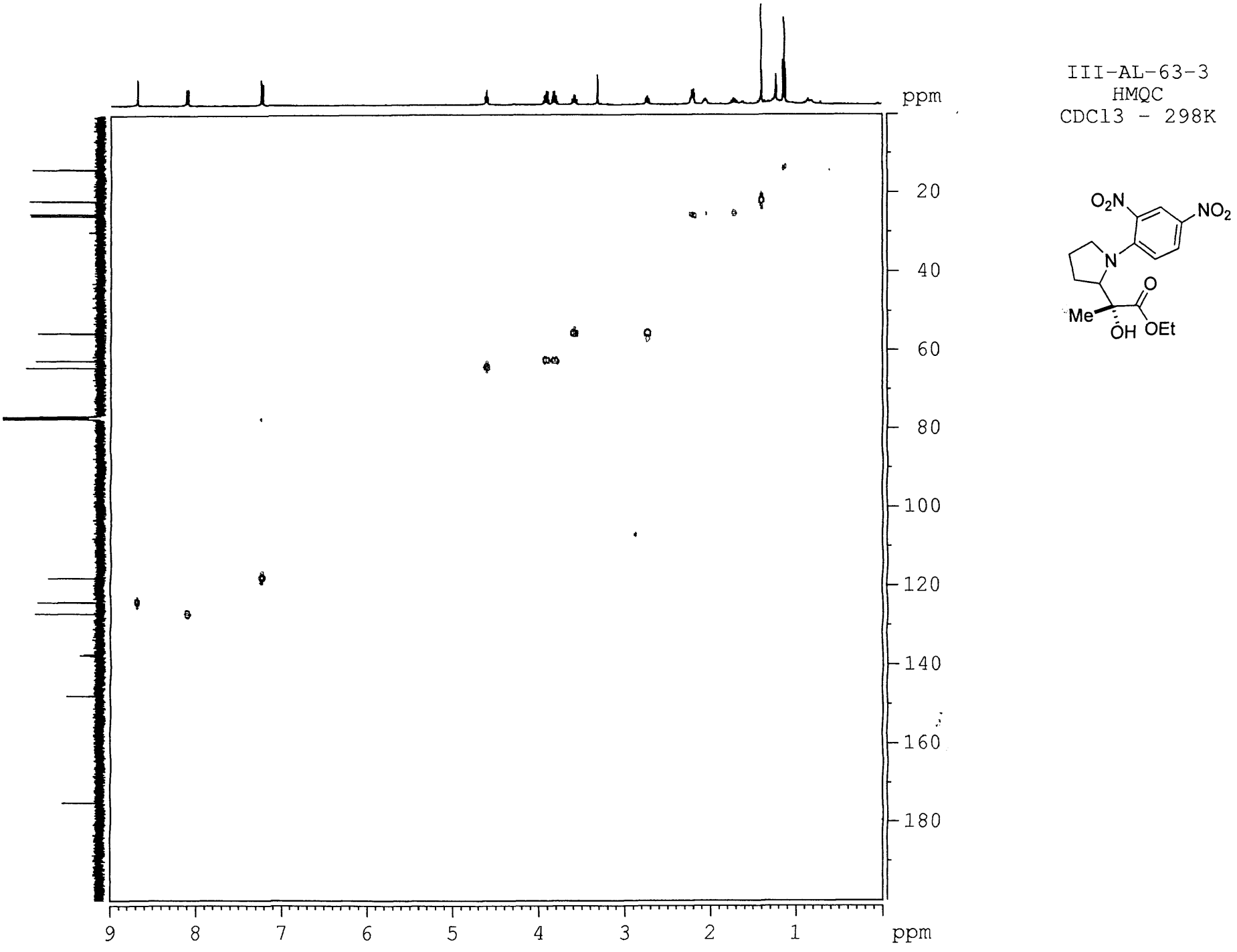


III-AL-63-3
COSY
CDCl3 - 298K

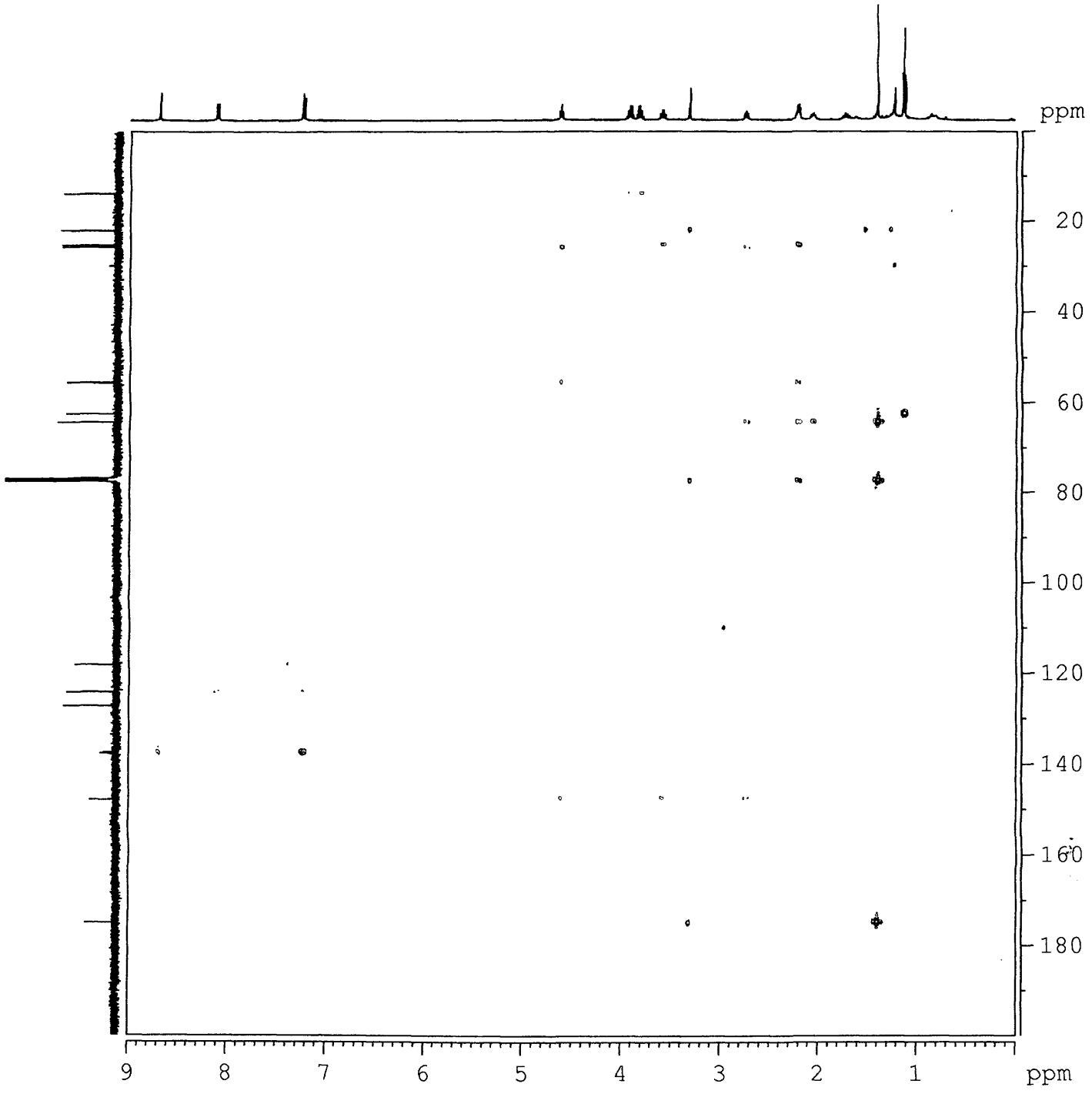


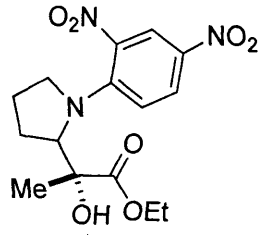


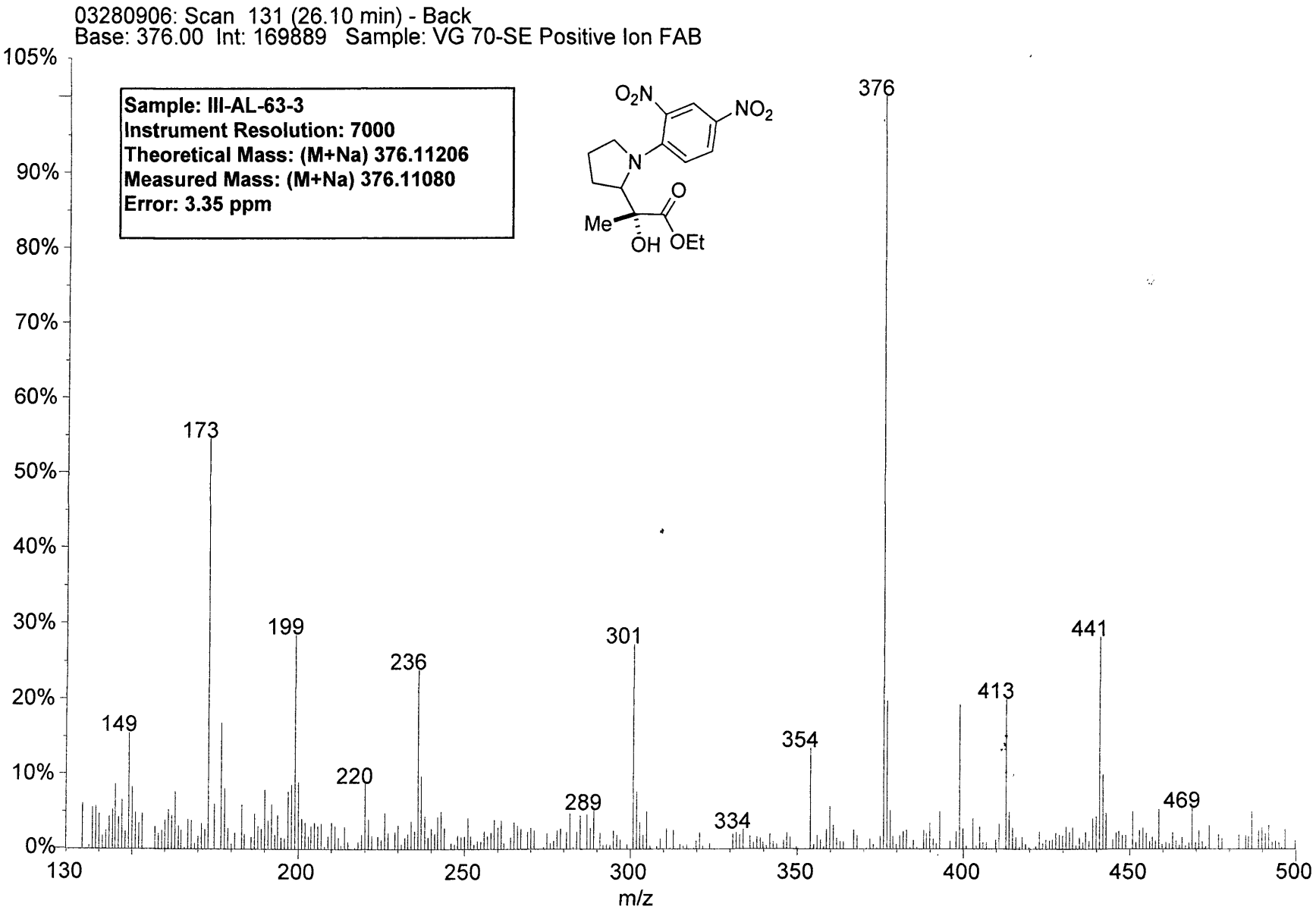
III-AL-63-3
HMQC
CDCl3 - 298K



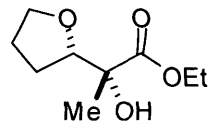
III-AL-63-3
HMBC
CDCl3 - 298K



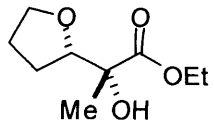


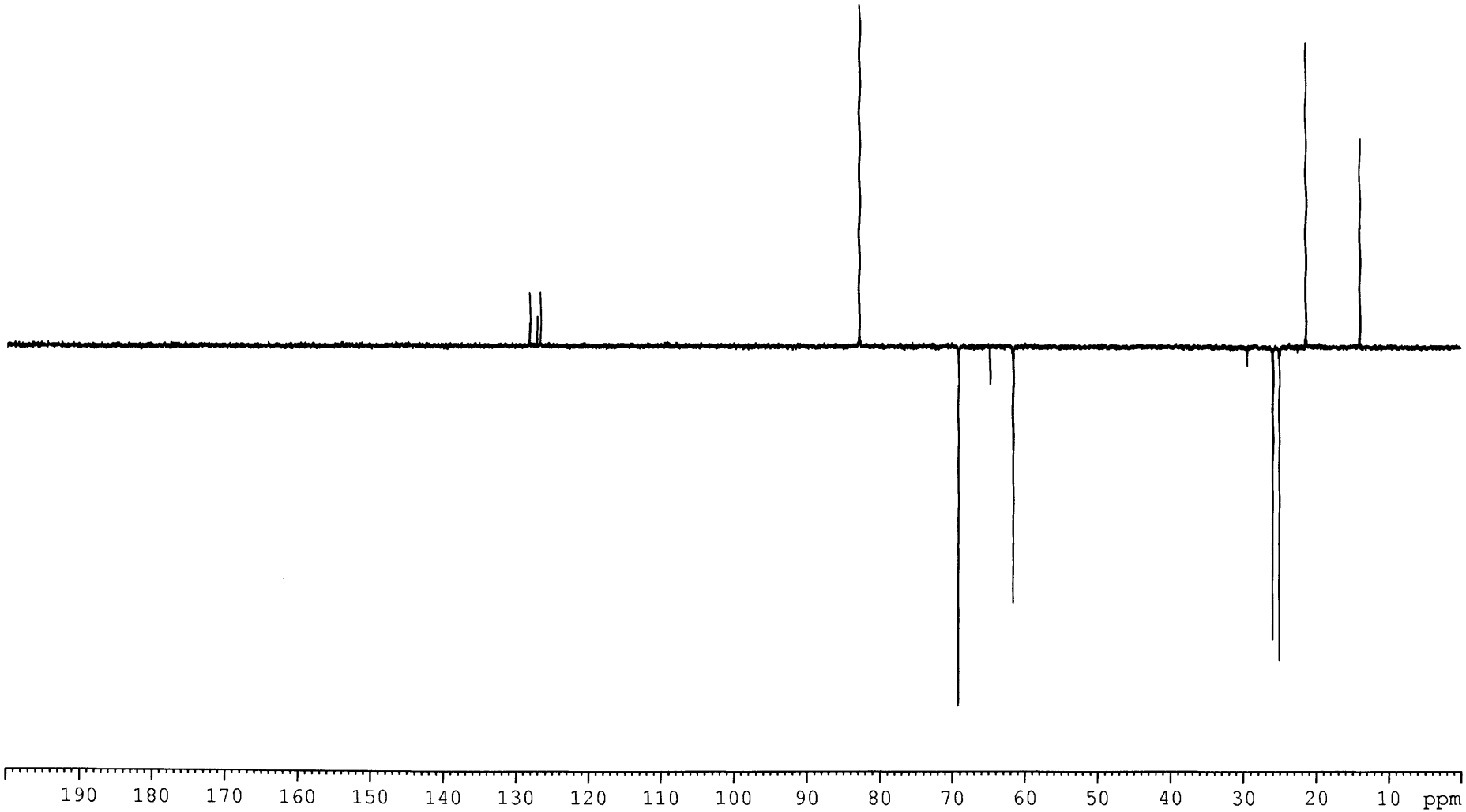

03280906: Scan 131 (26.10 min) - Back
Base: 376.00 Int: 169889 Sample: VG 70-SE Positive Ion FAB
Sample: III-AL-63-3
Instrument Resolution: 7000
Theoretical Mass: (M+Na) 376.11206
Measured Mass: (M+Na) 376.11080
Error: 3.35 ppm
O2N
NO2
N
O
Me
OH
OEt
105%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
376
173
199
236
301
441
413
149
354
220
289
334
469
130
200
250
300
350
400
450
500
m/z

III-AL-95-3
CDCl3 - 298K

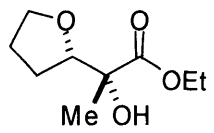


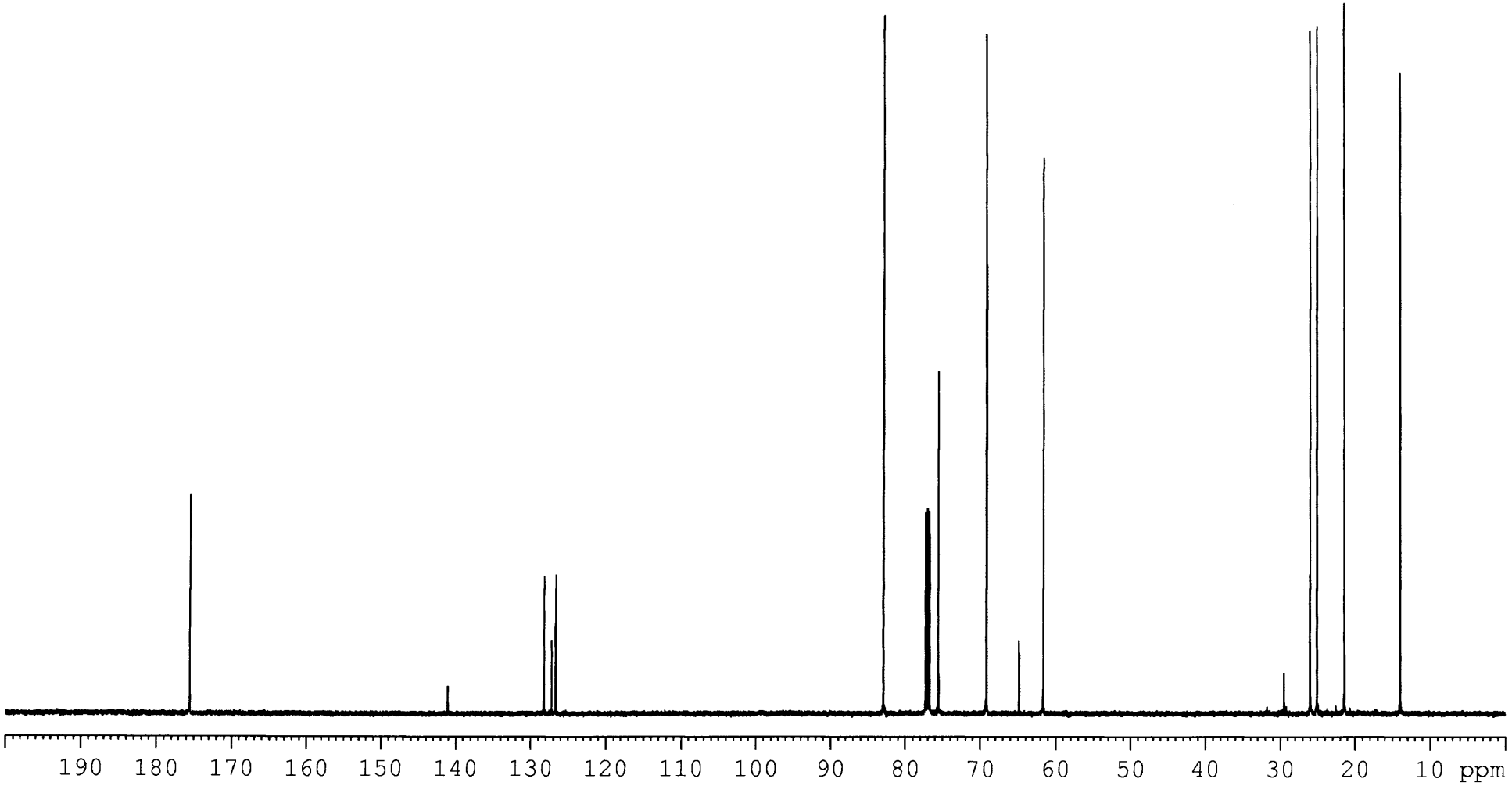
III-AL-95-3
DEPT
CDCl3 - 298K



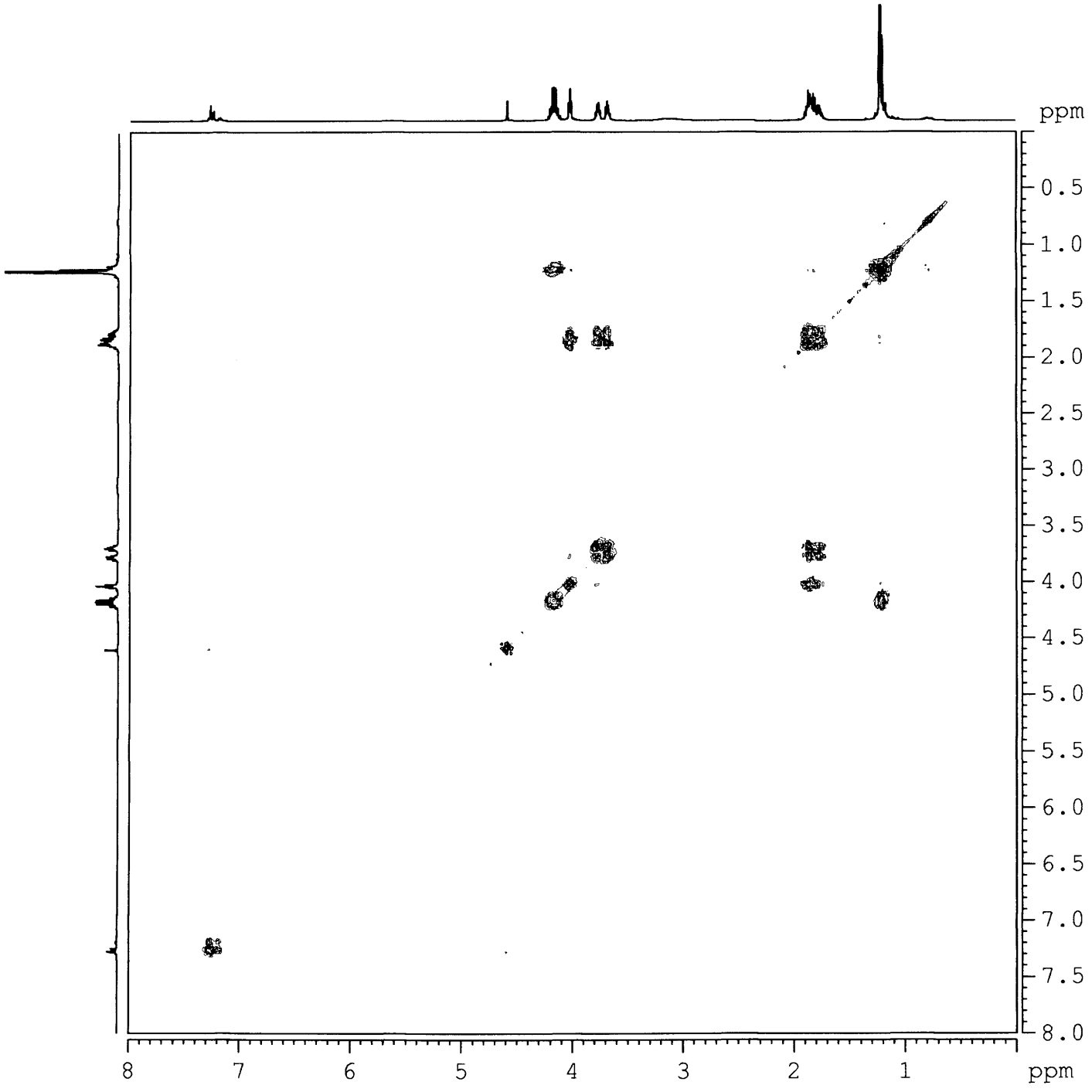


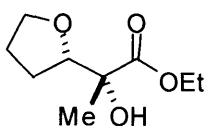
III-AL-95-3
13C
CDCl3 - 298K



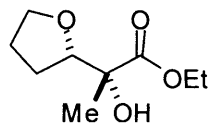


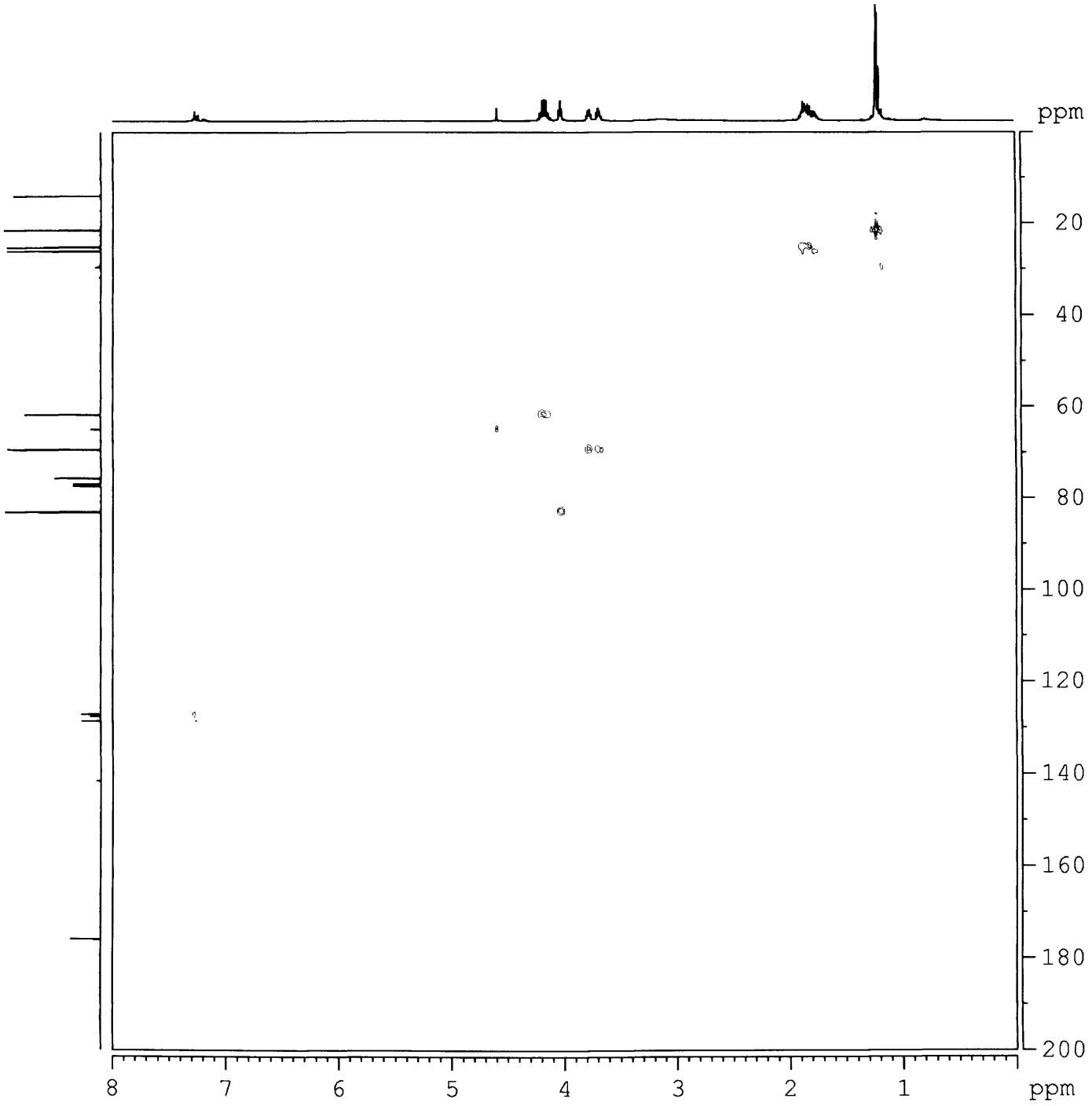
III-AL-95-3
cosy
CDCl3 - 298K

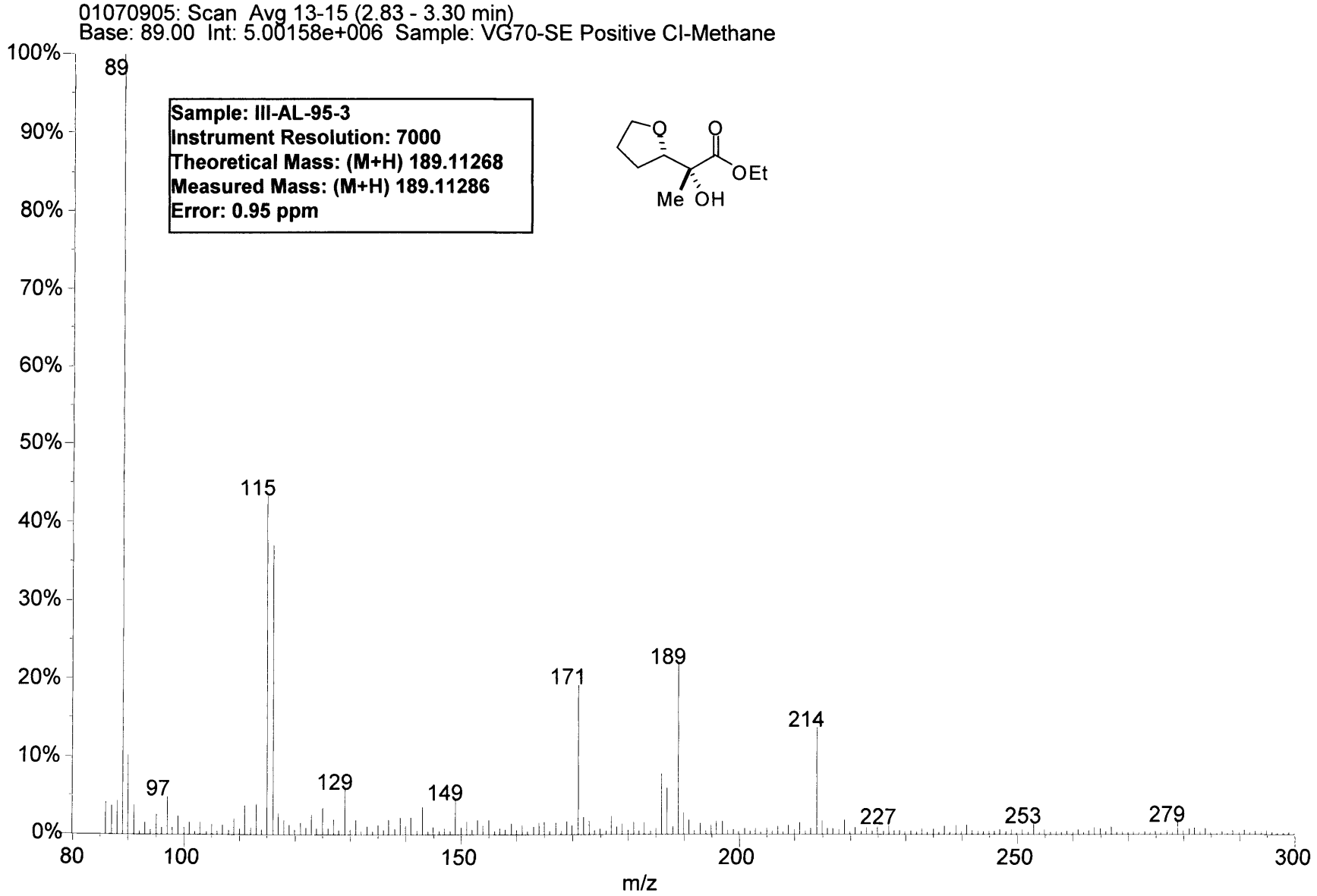


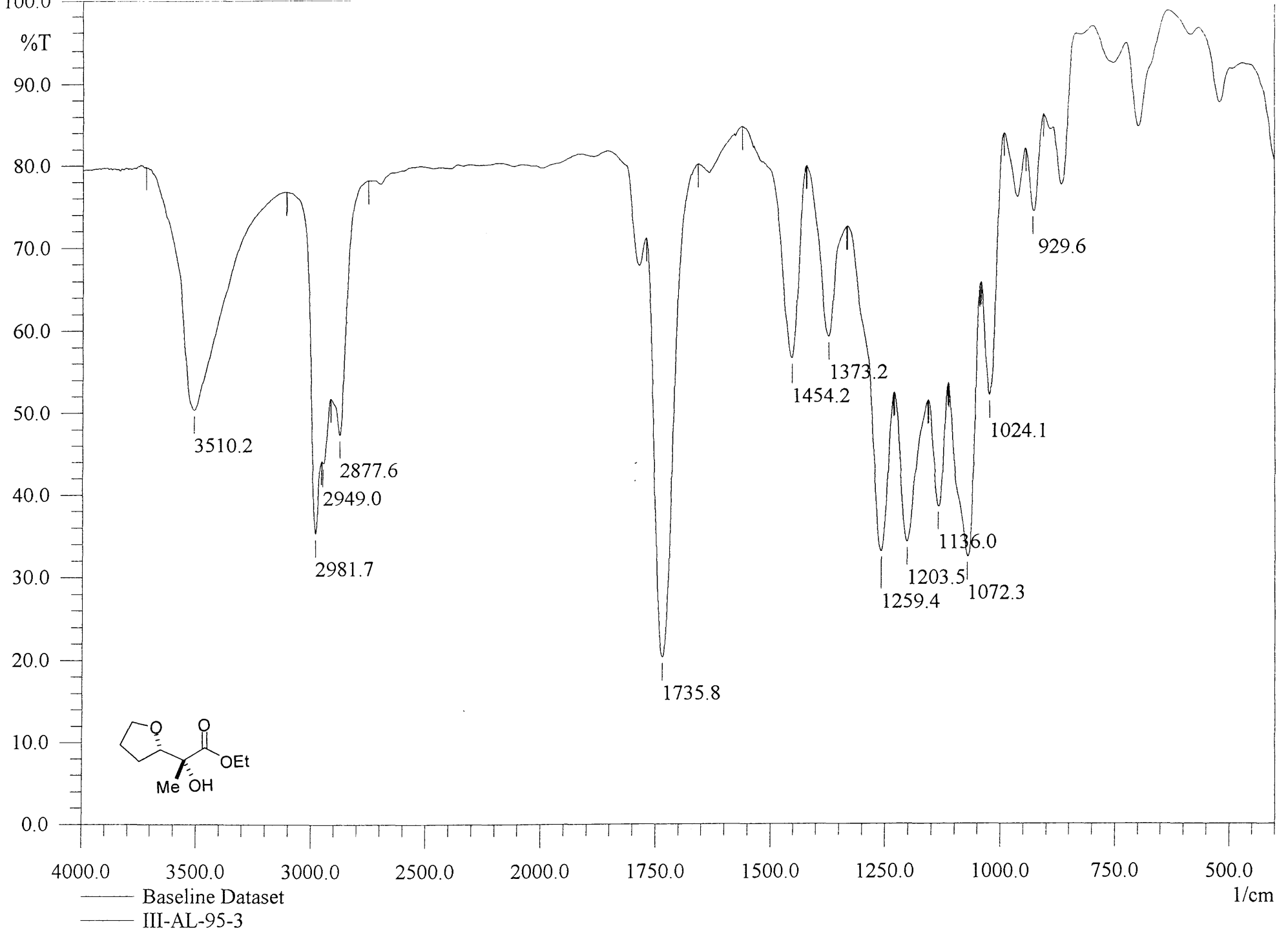


III-AL-95-3
HMQC
CDCl3 - 298K

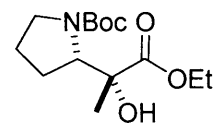




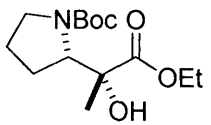

01070905: Scan Avg 13-15 (2.83 - 3.30 min)
Base: 89.00 Int: 5.00158e+006 Sample: VG70-SE Positive CI-Methane
Sample: III-AL-95-3
Instrument Resolution: 7000
Theoretical Mass: (M+H) 189.11268
Measured Mass: (M+H) 189.11286
Error: 0.95 ppm
O
O
OEt
Me OH
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
89
115
97
129
149
171
189
214
227
253
279
80
100
150
200
250
300
m/z


100.0
%T
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
3510.2
2877.6
2949.0
2981.7
1735.8
1454.2
1373.2
1259.4
1203.5
1136.0
1072.3
1024.1
929.6
O
O
OEt
Me OH
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
Baseline Dataset
III-AL-95-3

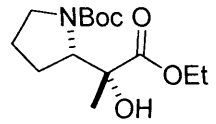
III-AL-102
CDCl3 - 298K

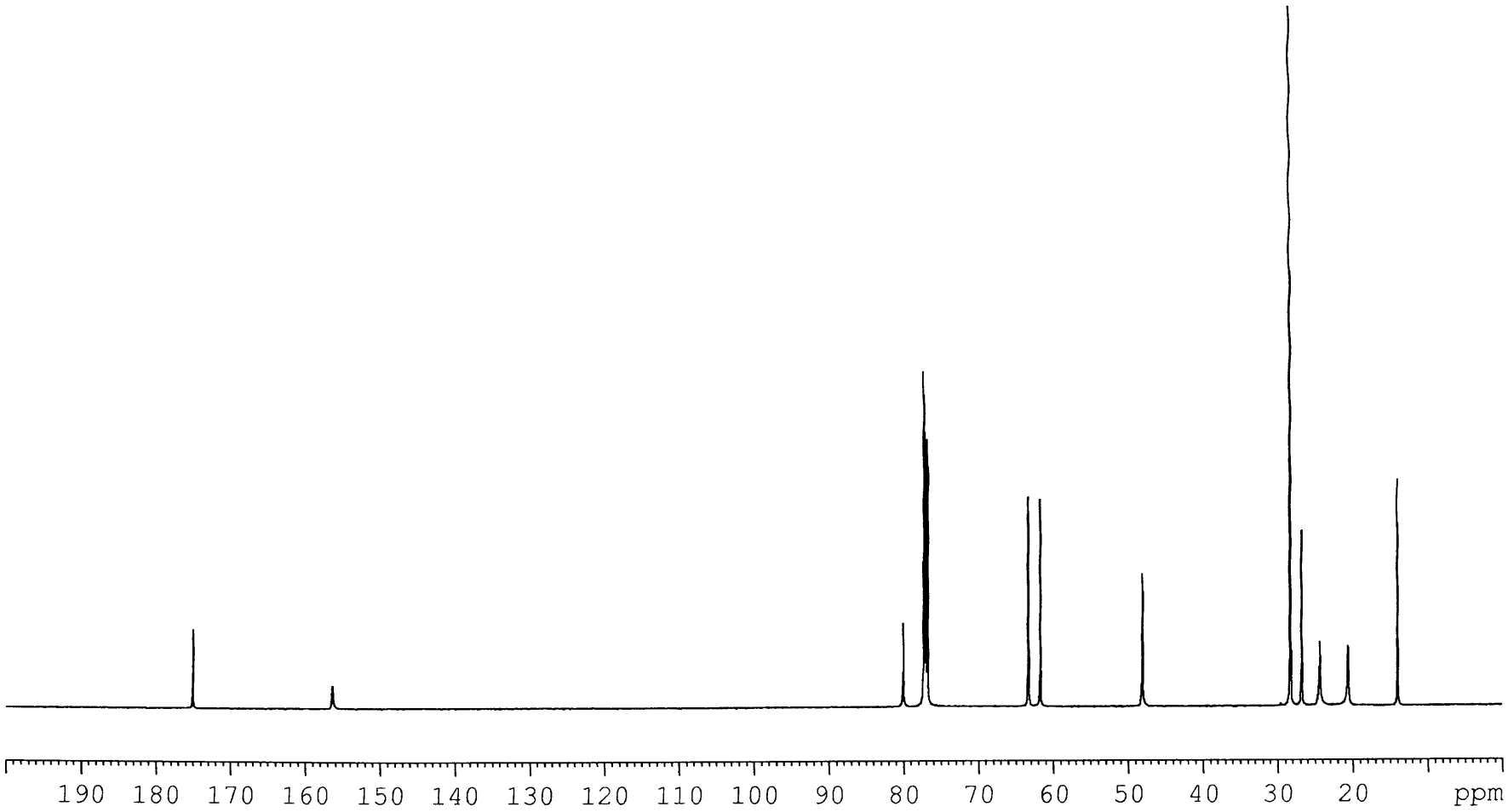


III-AL-102
dept
CDCl3 - 298K

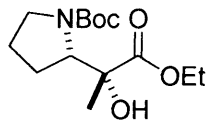


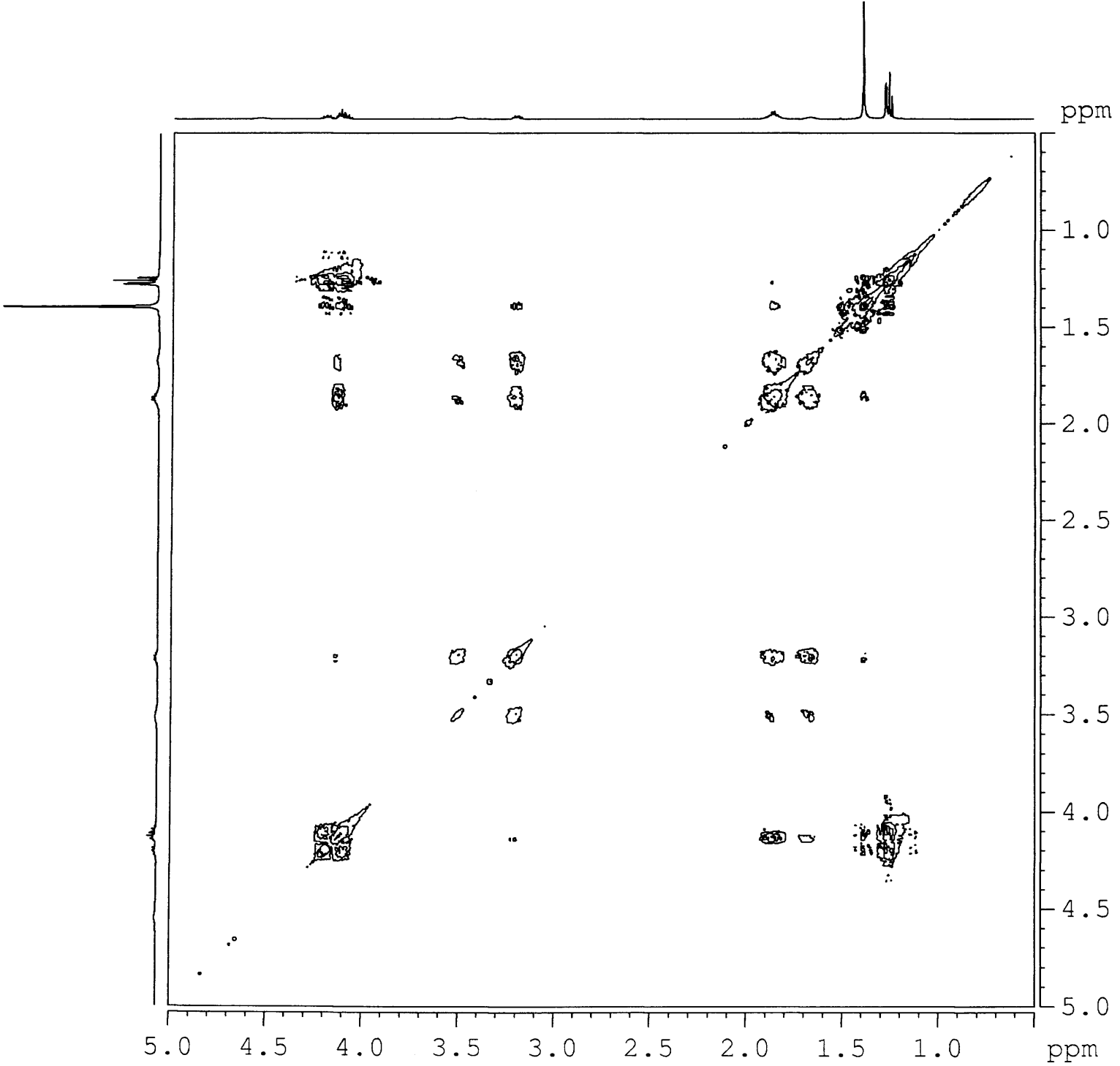
III-AL-102
13C
CDCl3 - 298K



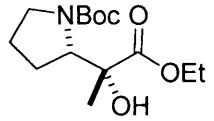


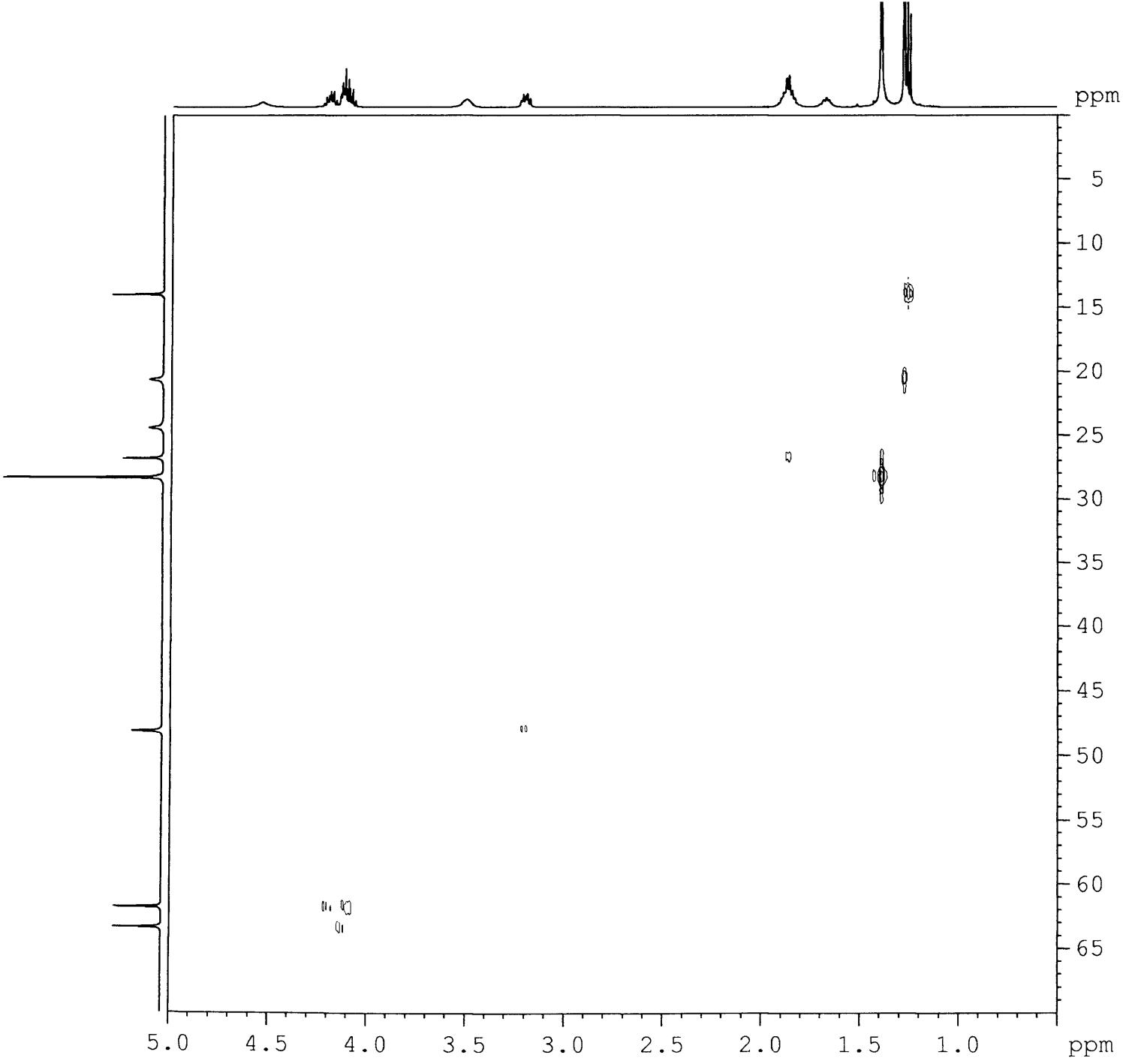
III-AL-102
COSY
CDCl3 - 298K

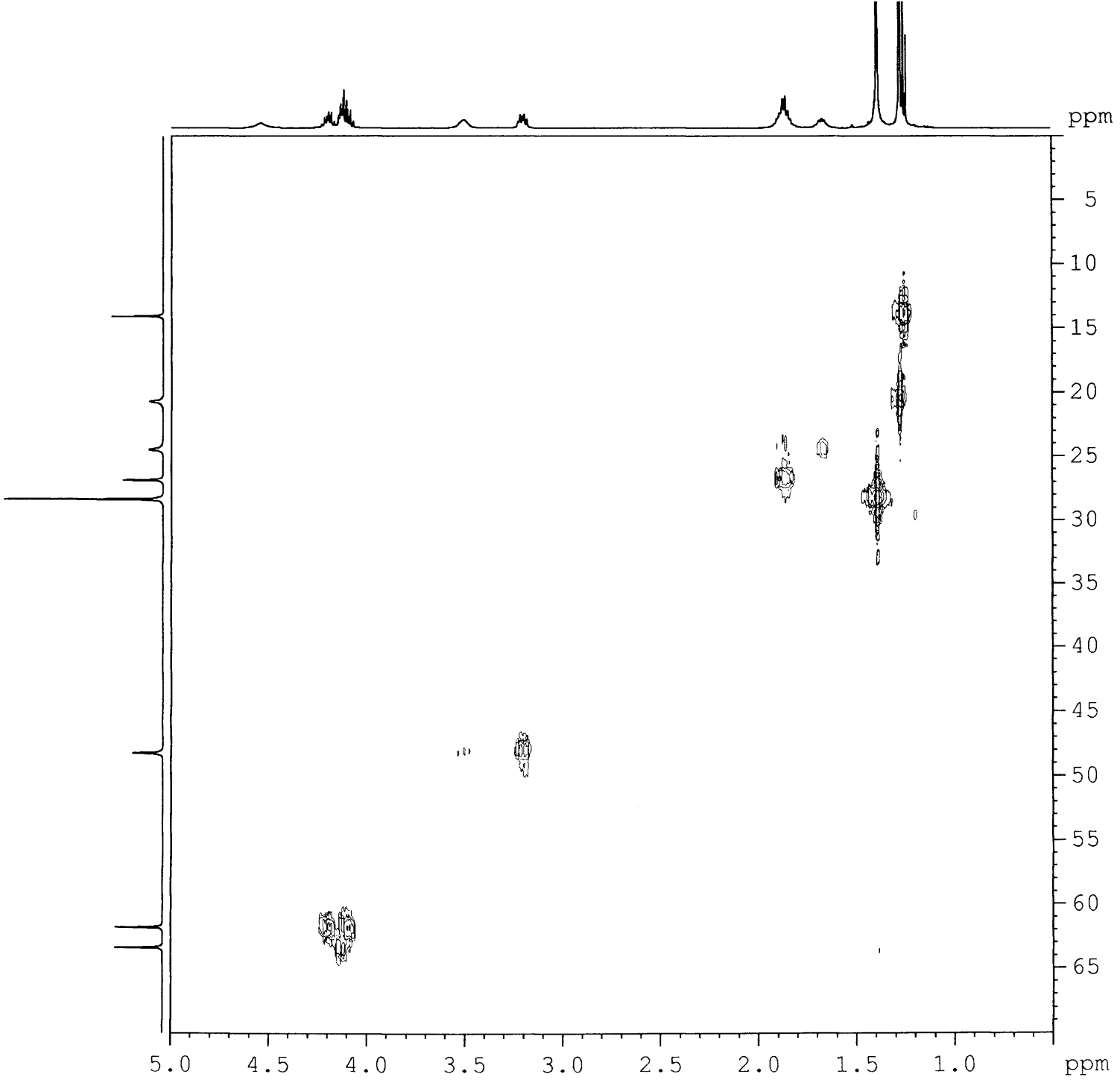




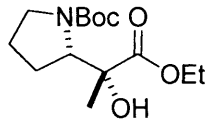
III-AL-102
HMQC
CDCl3 - 298K



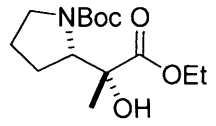


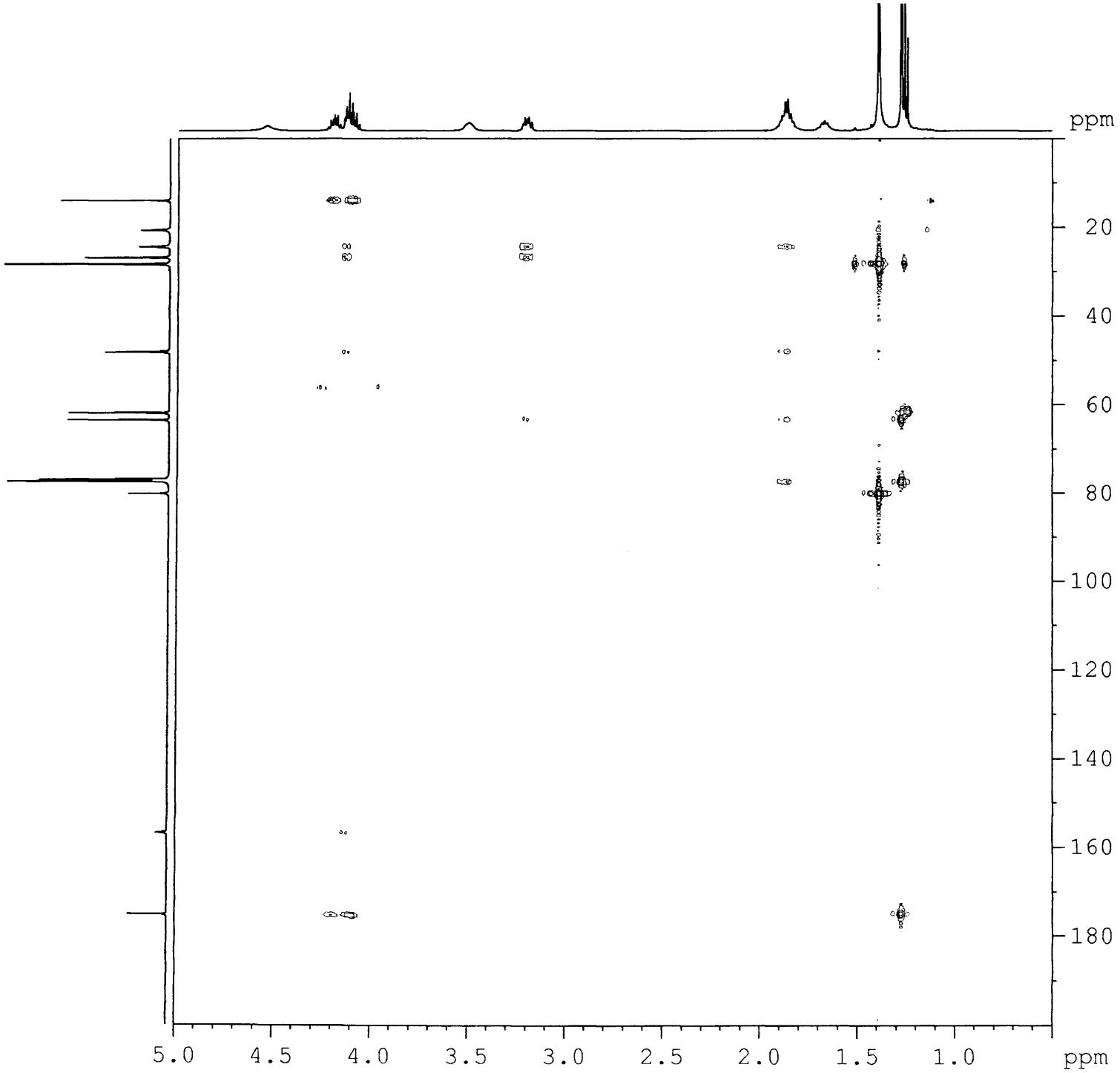


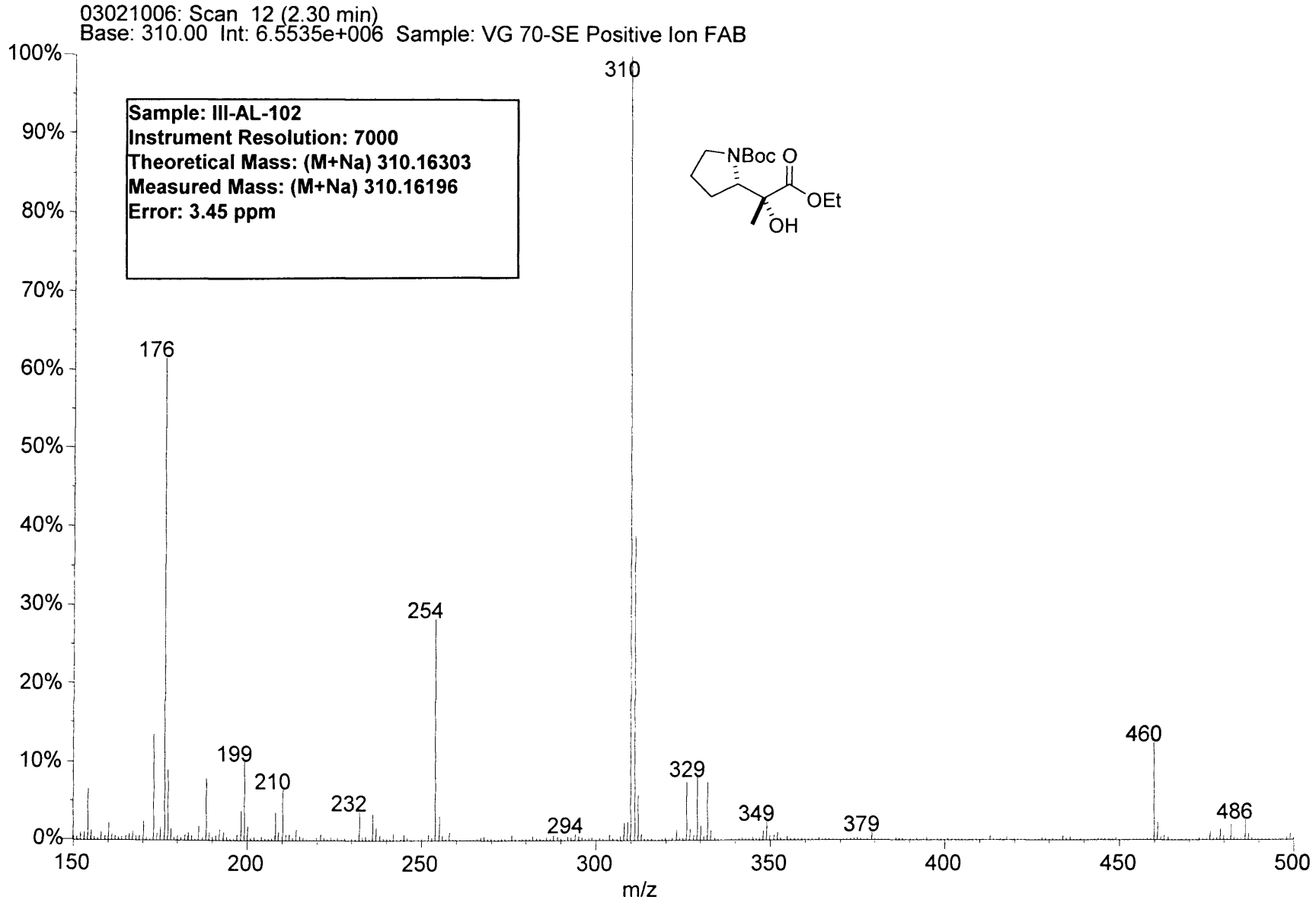
III-AL-102
HMQC
CDCl3 - 298K

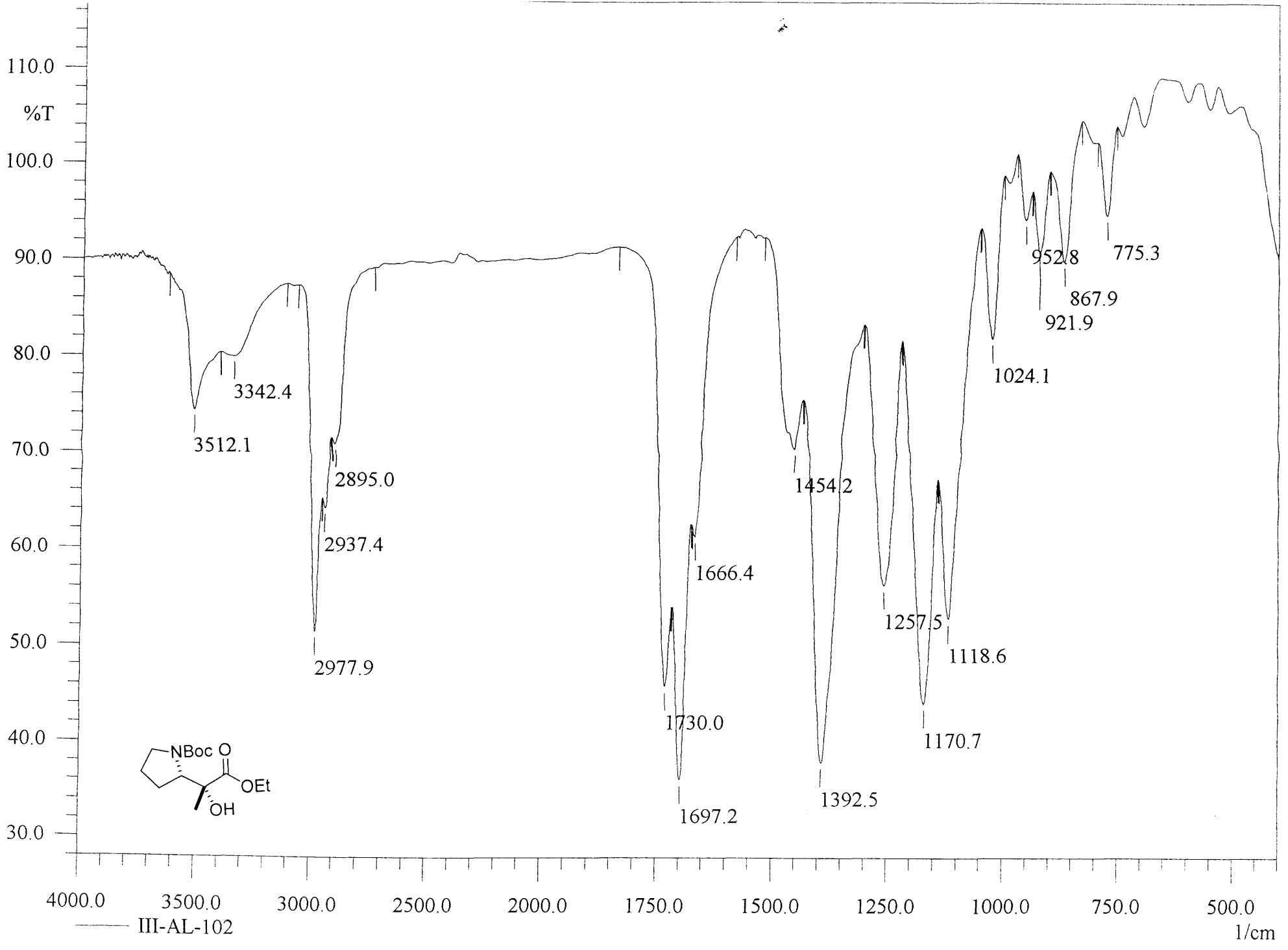


III-AL-102
HMBC
CDCl3 - 298K

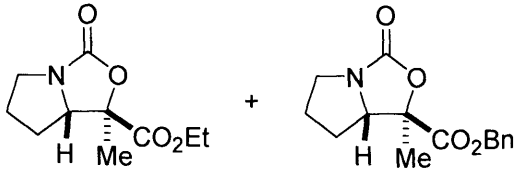





03021006: Scan 12 (2.30 min)
Base: 310.00 Int: 6.5535e+006 Sample: VG 70-SE Positive Ion FAB
Sample: III-AL-102
Instrument Resolution: 7000
Theoretical Mass: (M+Na) 310.16303
Measured Mass: (M+Na) 310.16196
Error: 3.45 ppm
NBoc O
OEt
OH
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
150
200
250
300
350
400
450
500
m/z
310
176
254
199
210
232
294
329
349
379
460
486

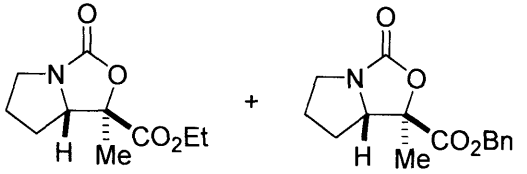

110.0
%T
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
3512.1
3342.4
2977.9
2937.4
2895.0
1730.0
1697.2
1666.4
1454.2
1392.5
1257.5
1170.7
1118.6
1024.1
952.8
921.9
867.9
775.3
NBoc
O
OEt
OH
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
III-AL-102

III-AL-177
CDCl3 - 298K

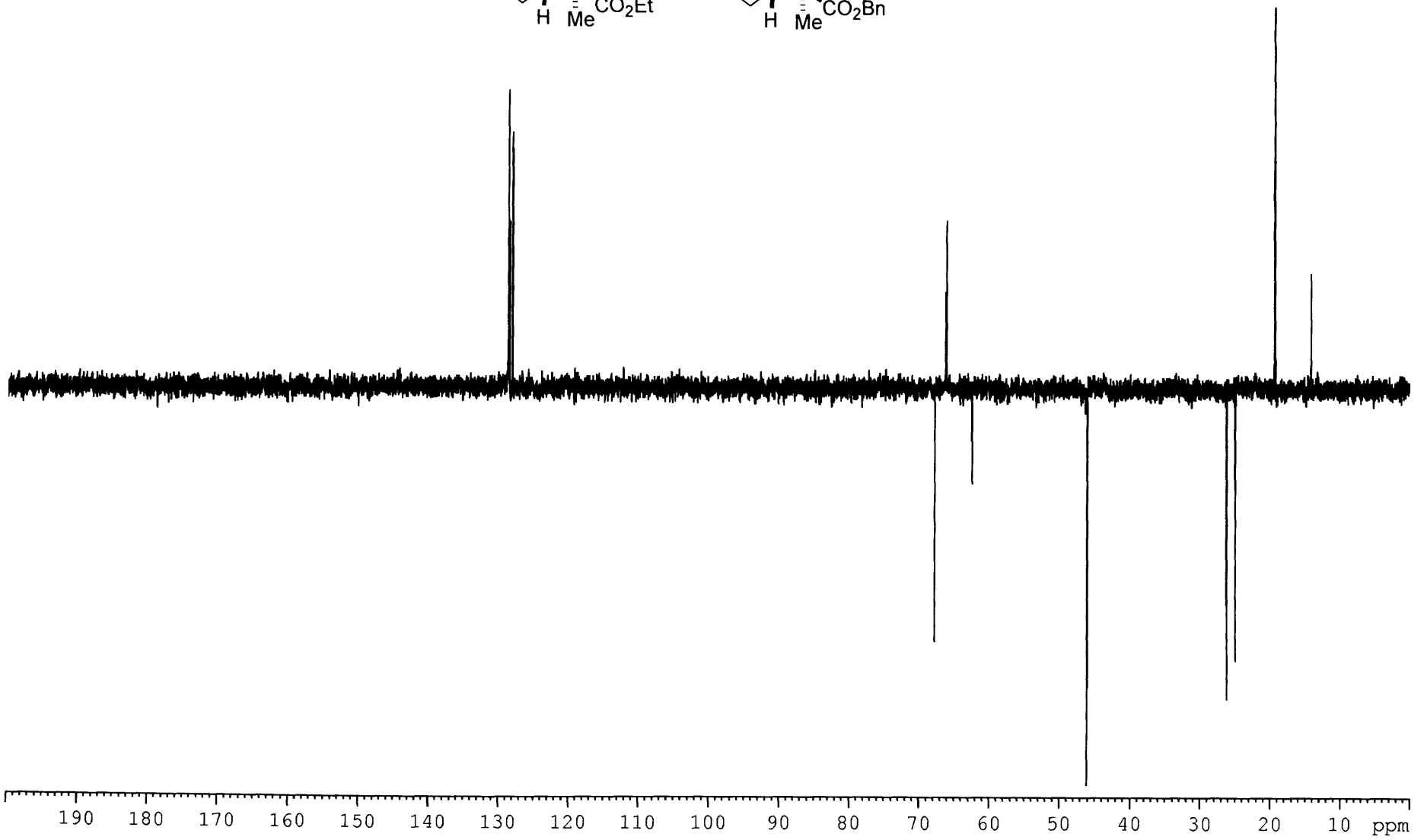


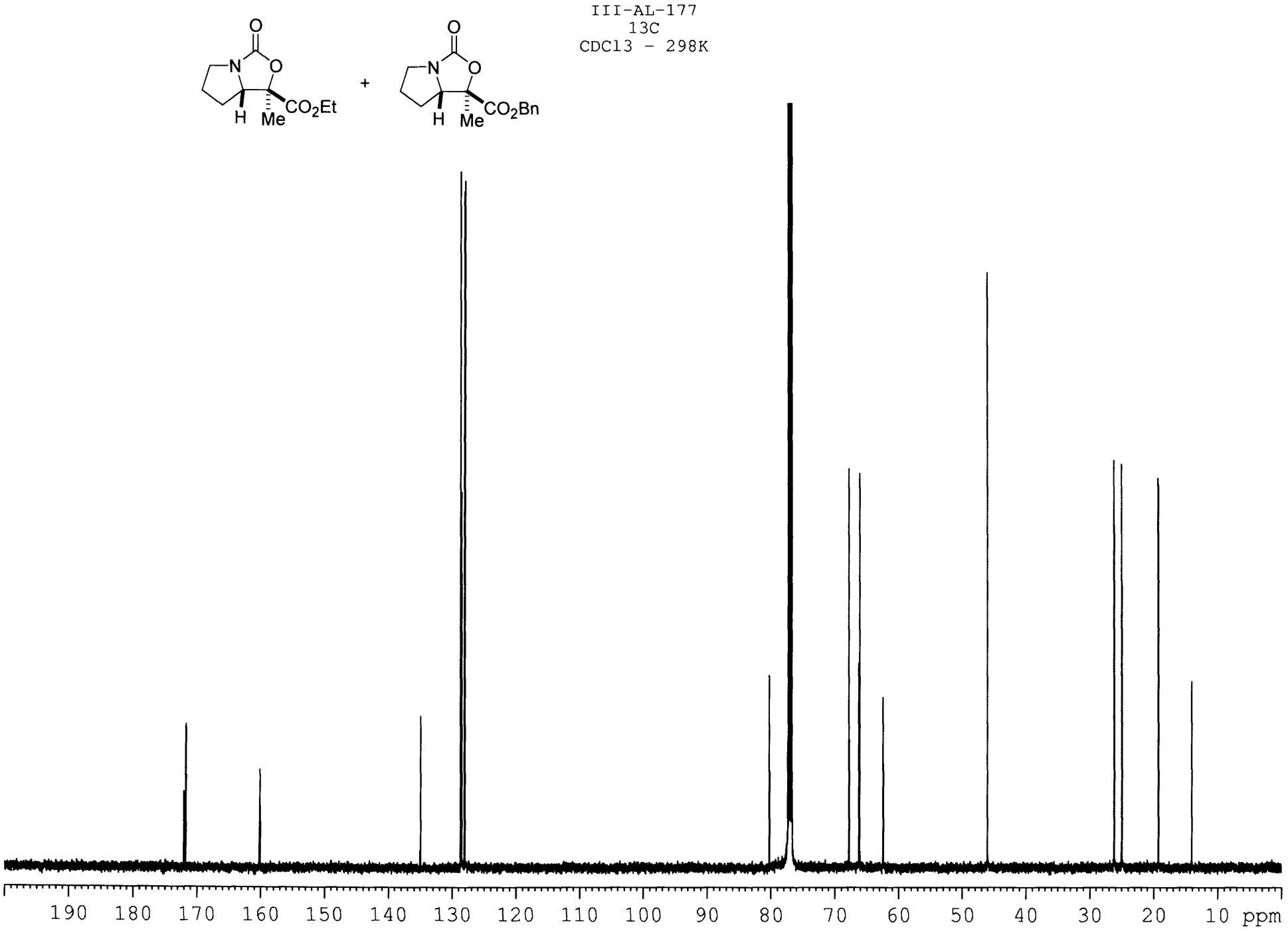
+

III-AL-177
DEPT
CDCl3 - 298K

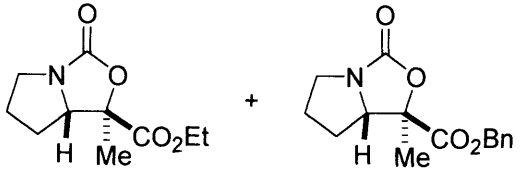


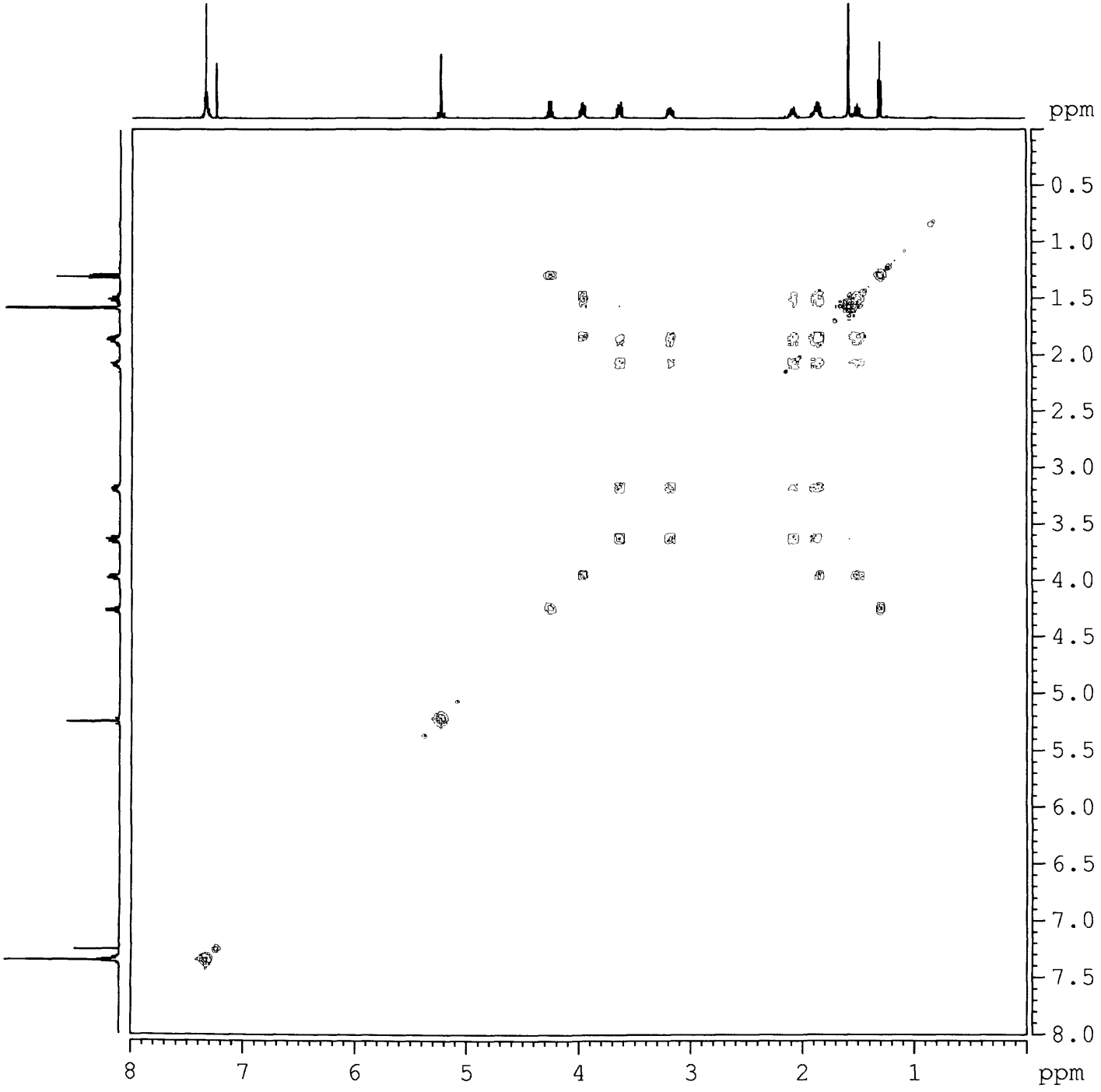
+



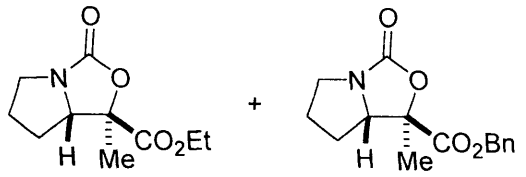

III-AL-177
13C
CDCl3 - 298K
O
N
O
H
Me
CO2Et
+
CO2Bn
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

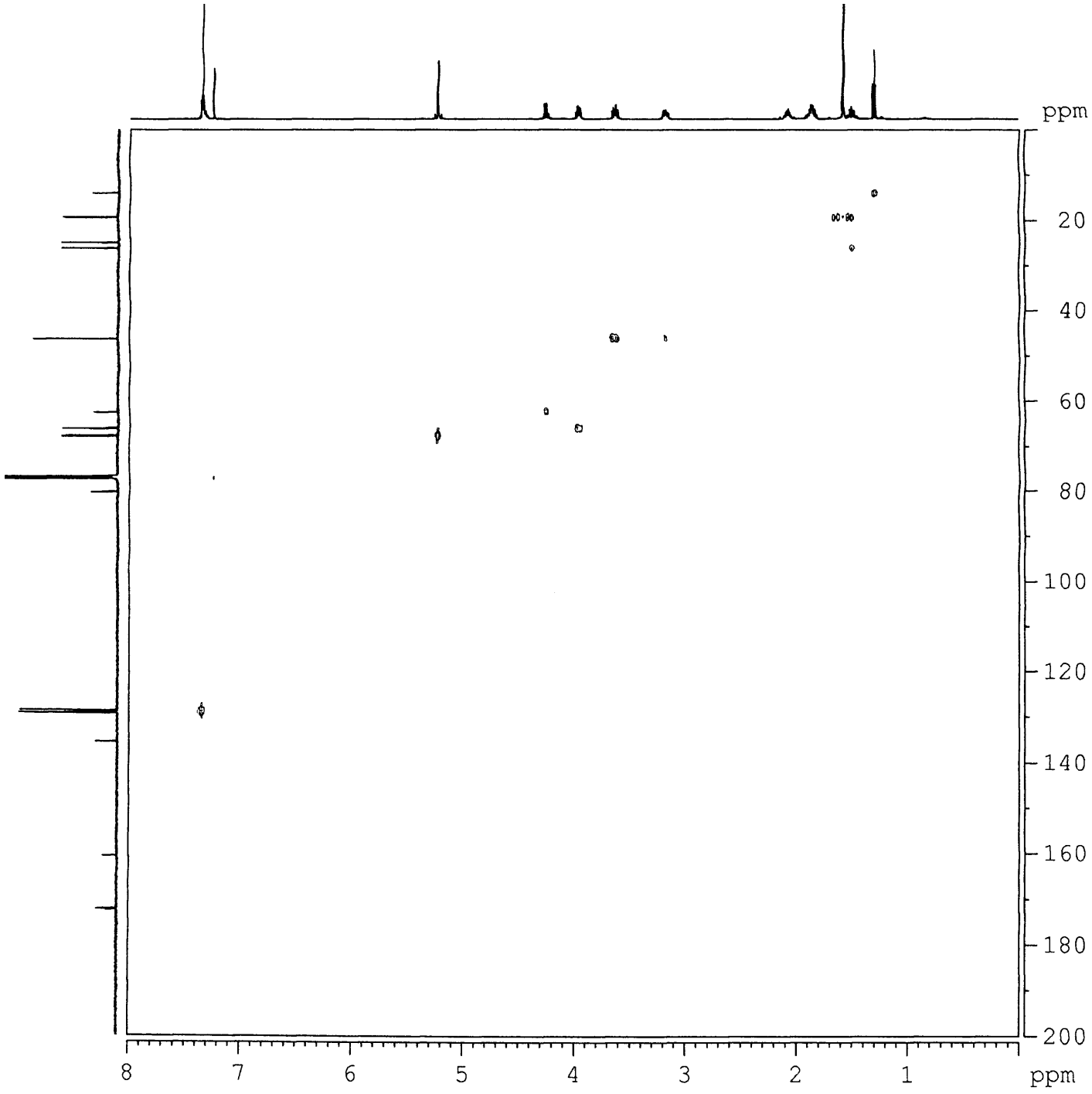
III-AL-177
COSY
CDCl3 - 298K



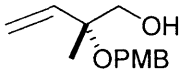


III-AL-177
HMQC
CDCl3 - 298K

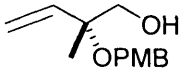


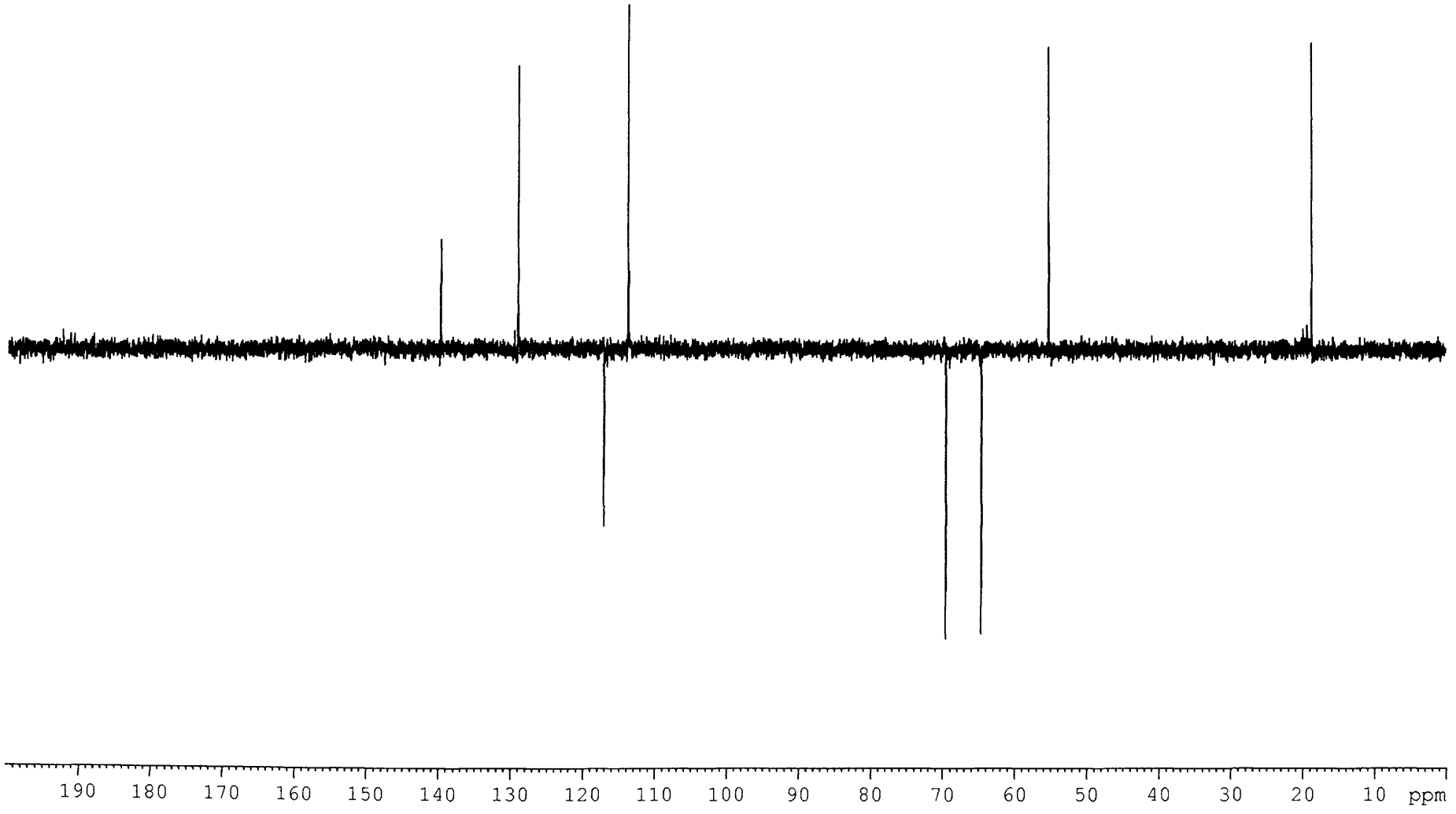


IV-AL-11
CDCl3 - 298K

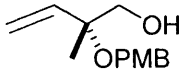


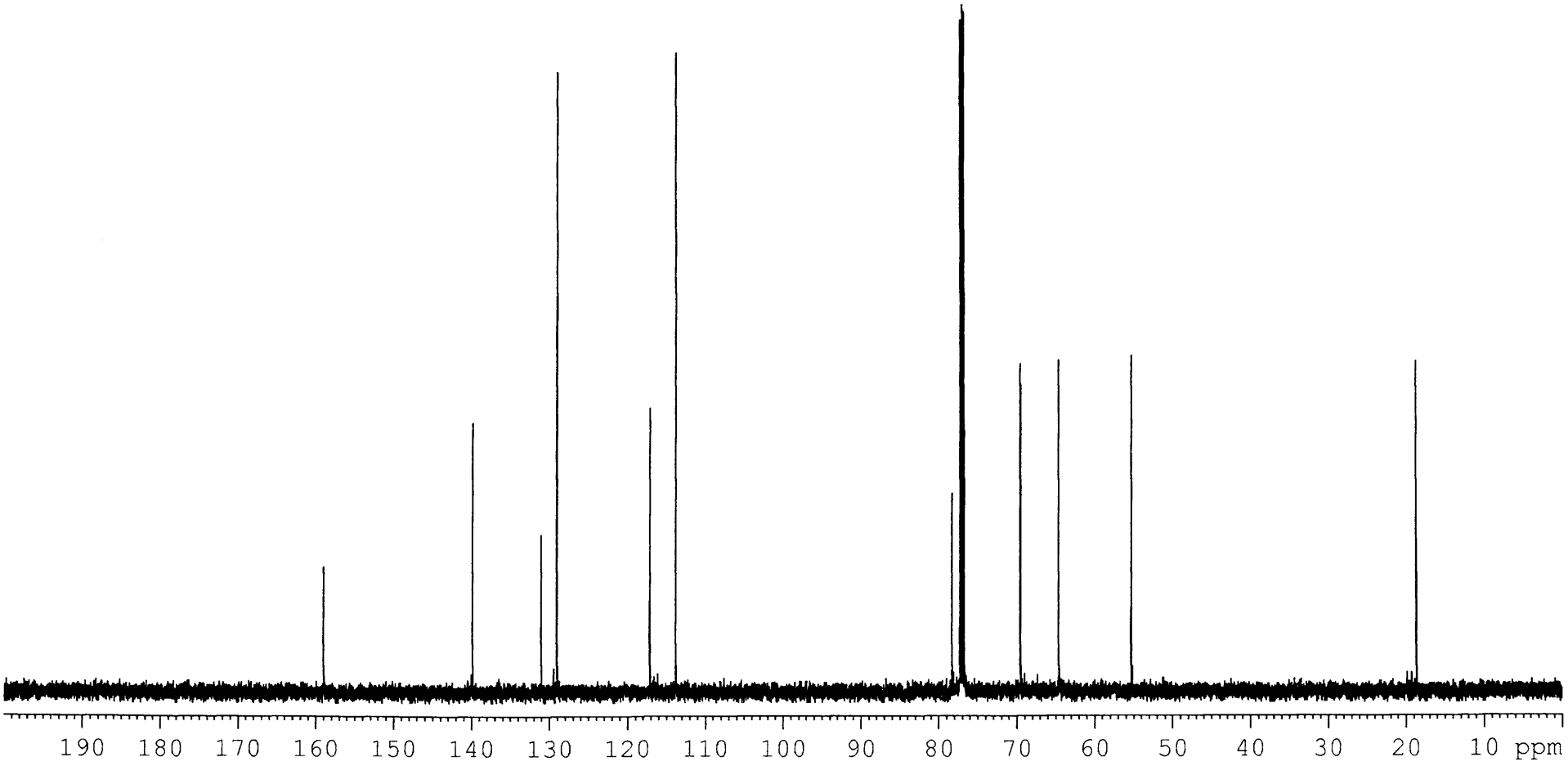
IV-AL-11
DEPT
CDCl3 - 298K

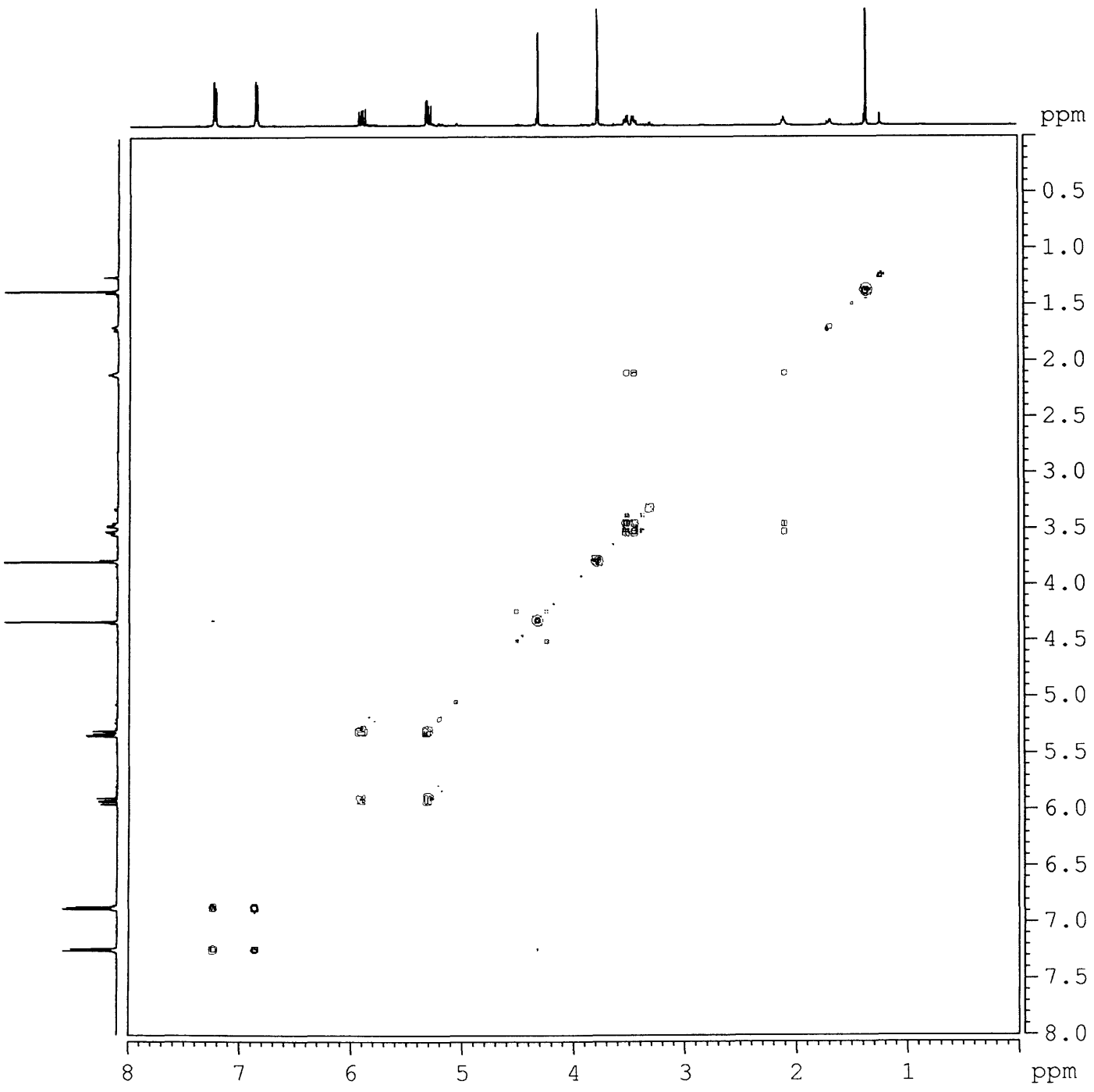




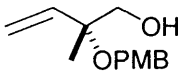
IV-AL-11
13C
CDCl3 - 298K

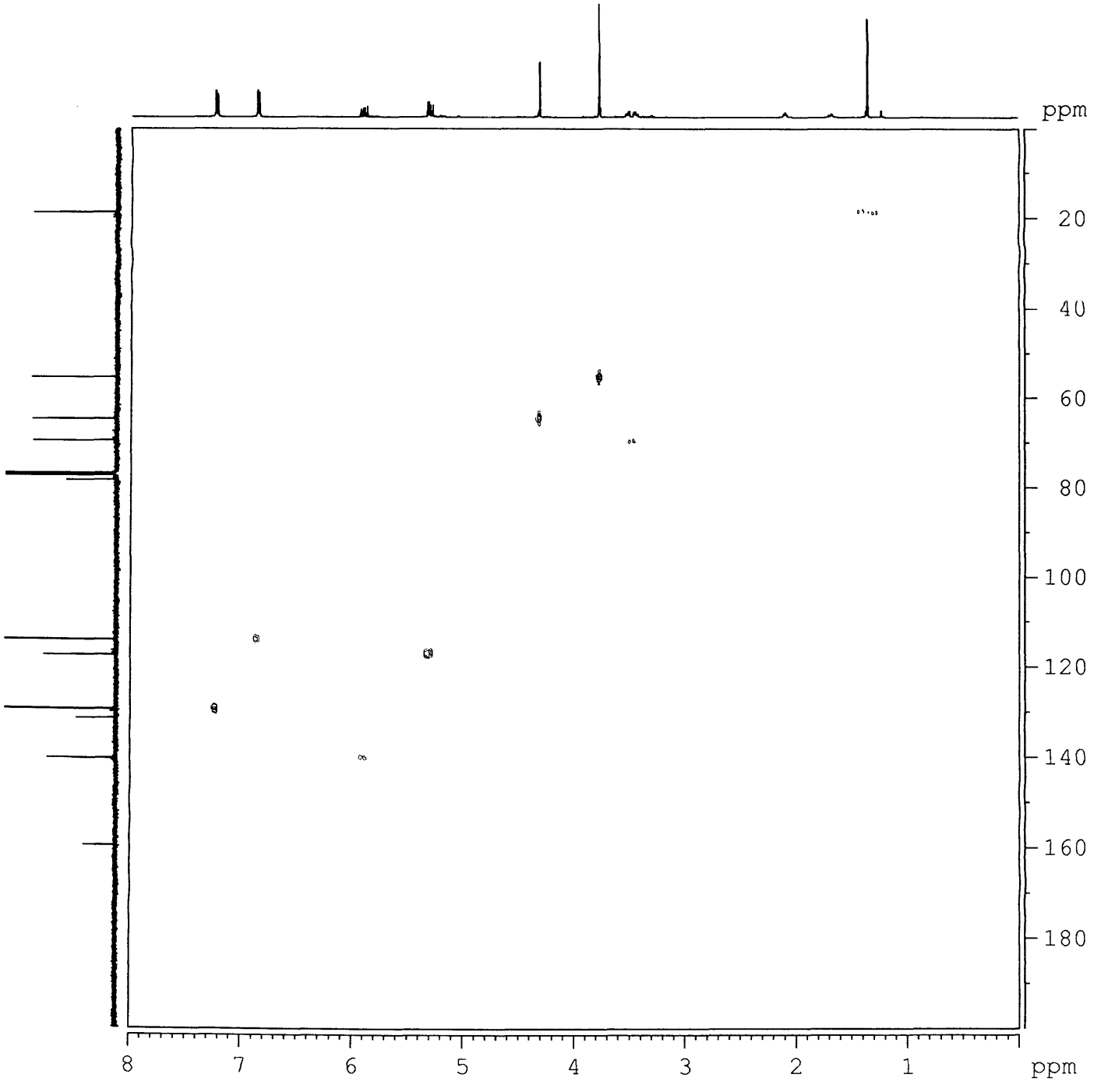




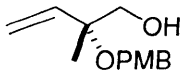


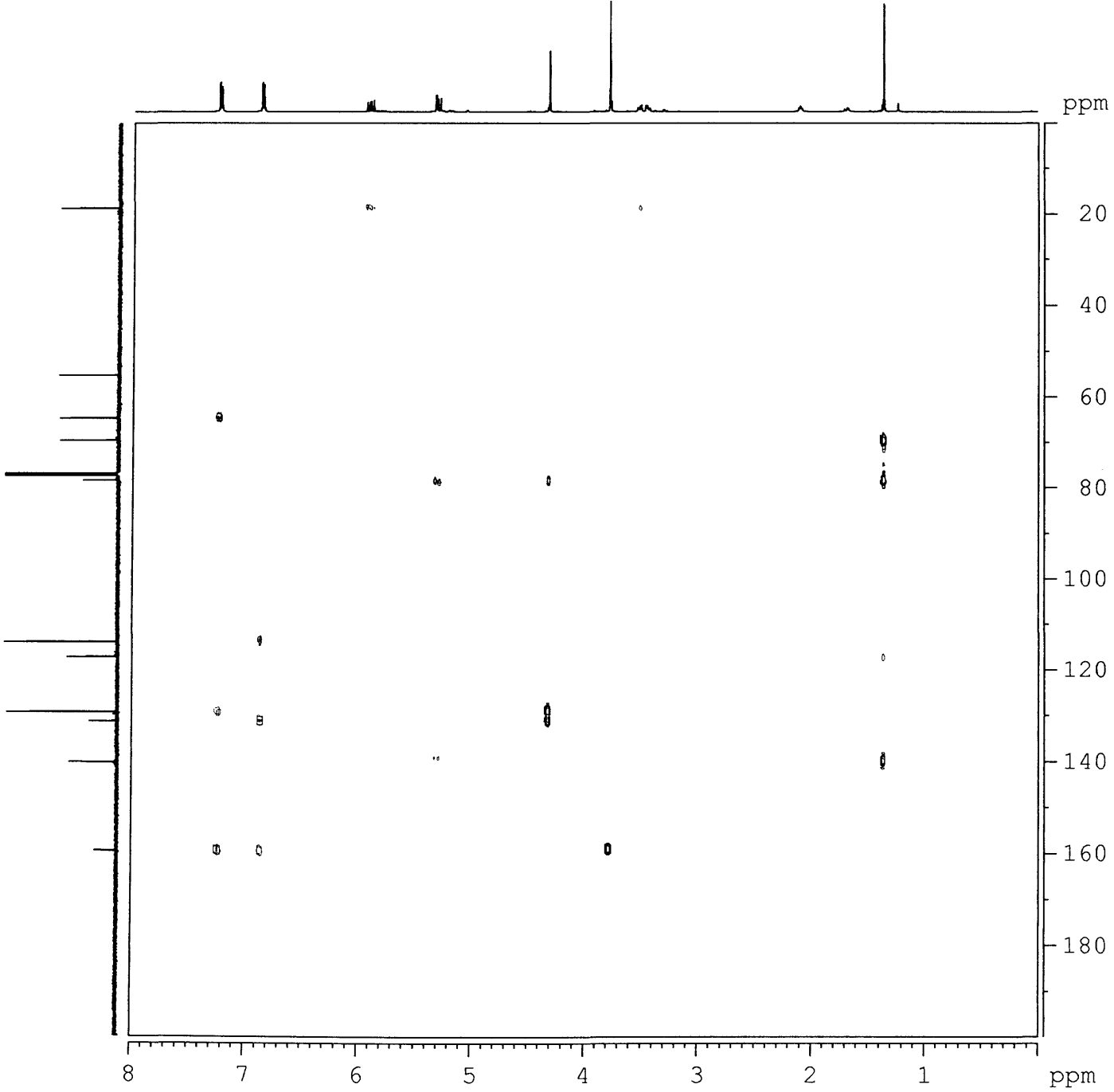
IV-AL-11
COSY
CDCl3 - 298K



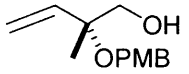


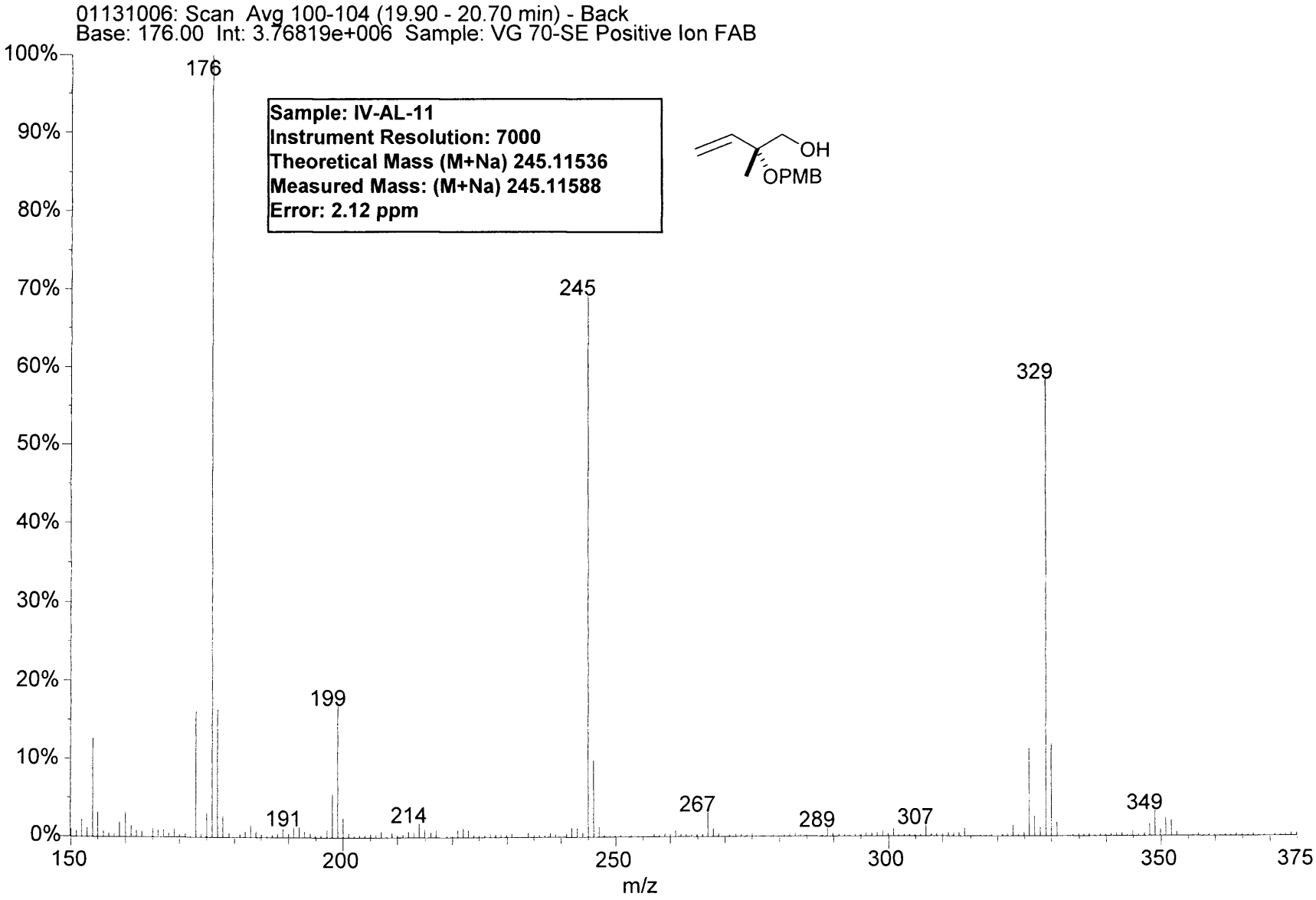
IV-AL-11
HMQC
CDCl3 - 298K

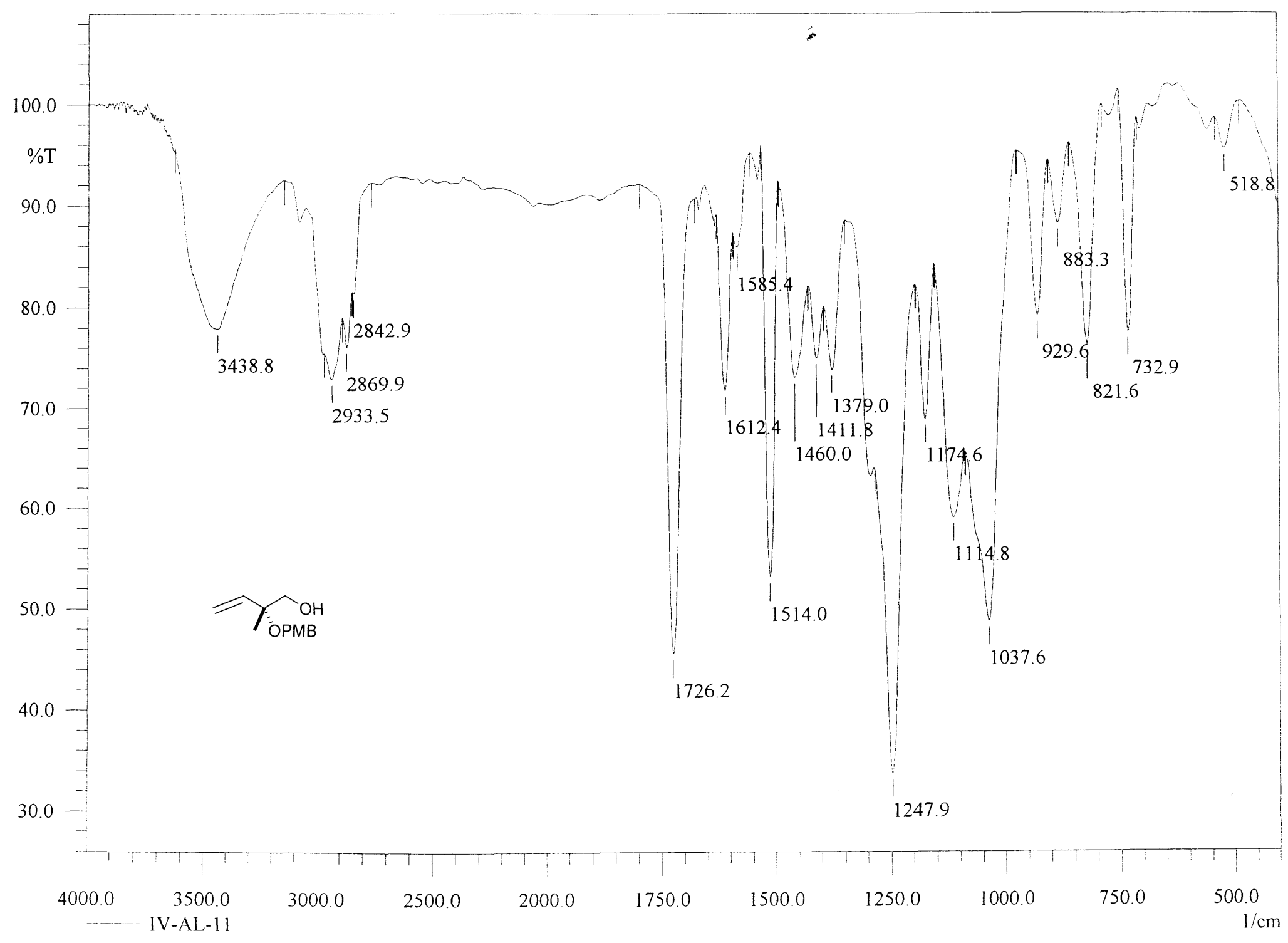


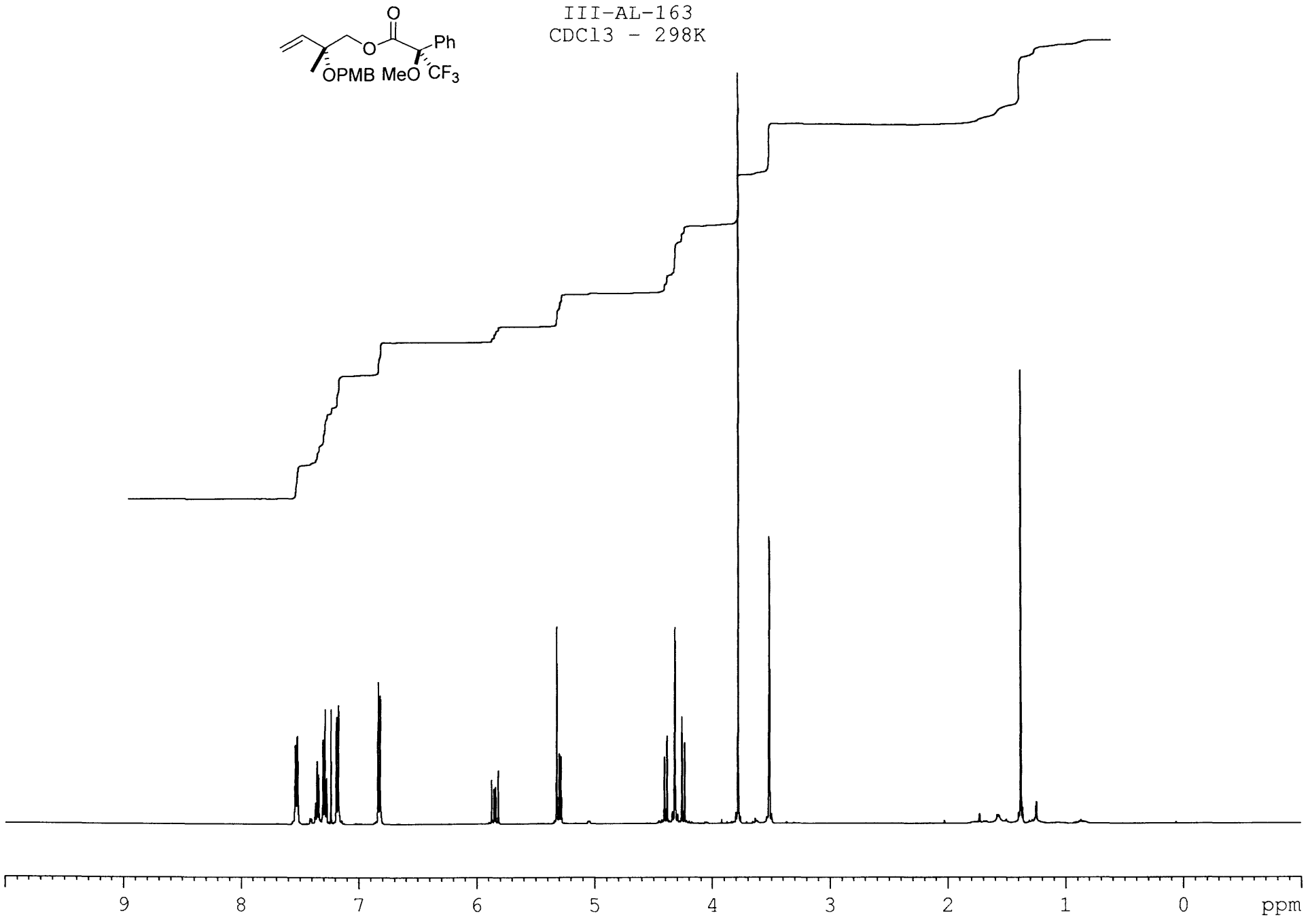


IV-AL-11
HMBC
CDC13 - 298K

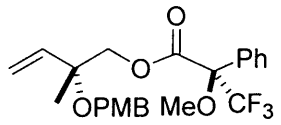


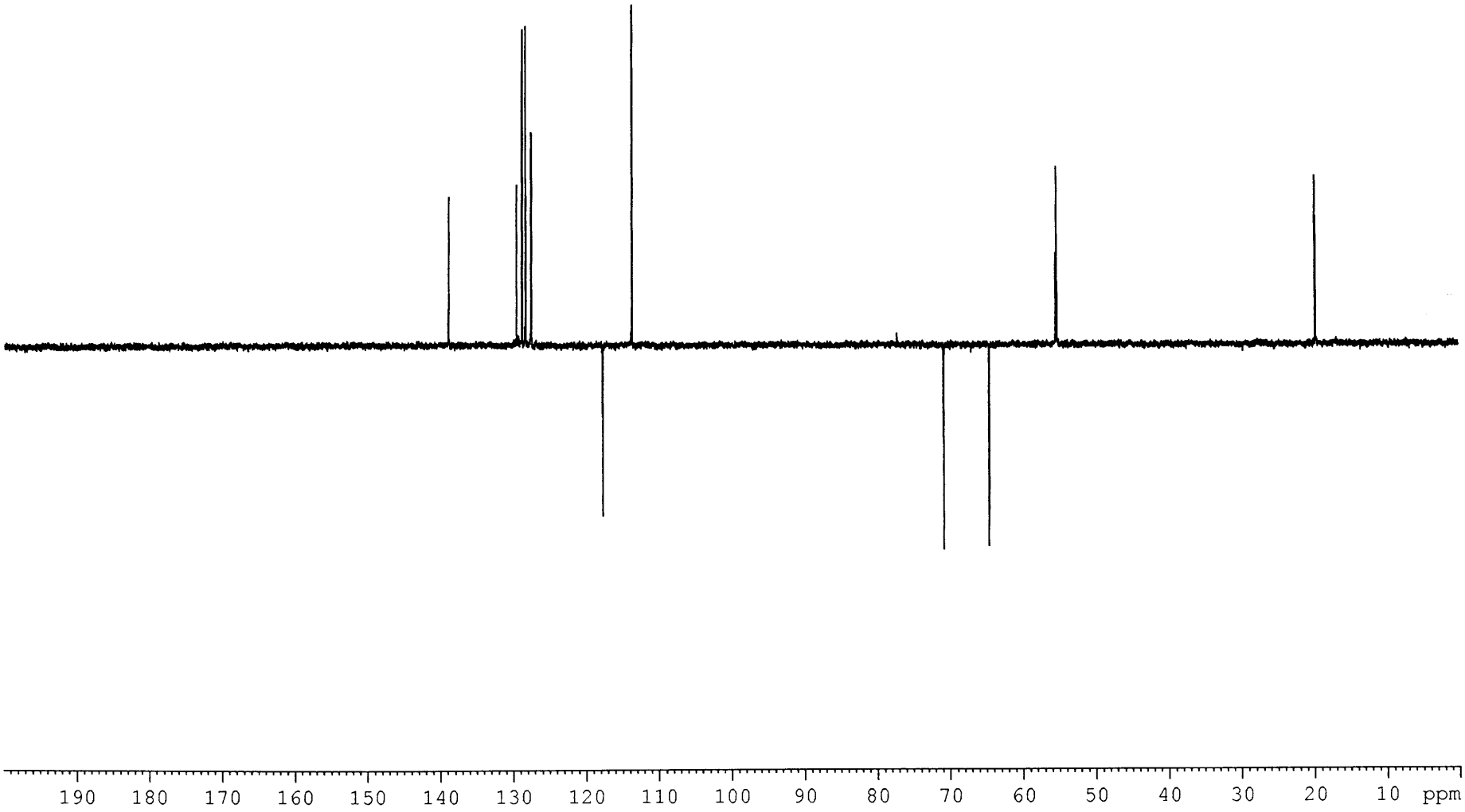

01131006: Scan Avg 100-104 (19.90 - 20.70 min) - Back
Base: 176.00 Int: 3.76819e+006 Sample: VG 70-SE Positive Ion FAB
Sample: IV-AL-11
Instrument Resolution: 7000
Theoretical Mass (M+Na) 245.11536
Measured Mass: (M+Na) 245.11588
Error: 2.12 ppm
OH
OPMB
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
176
245
329
199
191
214
267
289
307
349
150
200
250
300
350
375
m/z


100.0
%T
90.0
80.0
70.0
60.0
50.0
40.0
30.0
3438.8
2842.9
2869.9
2933.5
1585.4
1612.4
1460.0
1514.0
1379.0
1411.8
1726.2
1247.9
1174.6
1114.8
1037.6
883.3
929.6
821.6
732.9
518.8
OH
OPMB
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
IV-AL-11

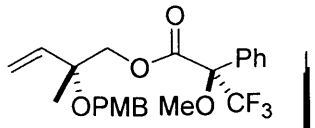

III-AL-163
CDCl3 - 298K
O
Ph
OPMB MeO CF3
9
8
7
6
5
4
3
2
1
0
ppm

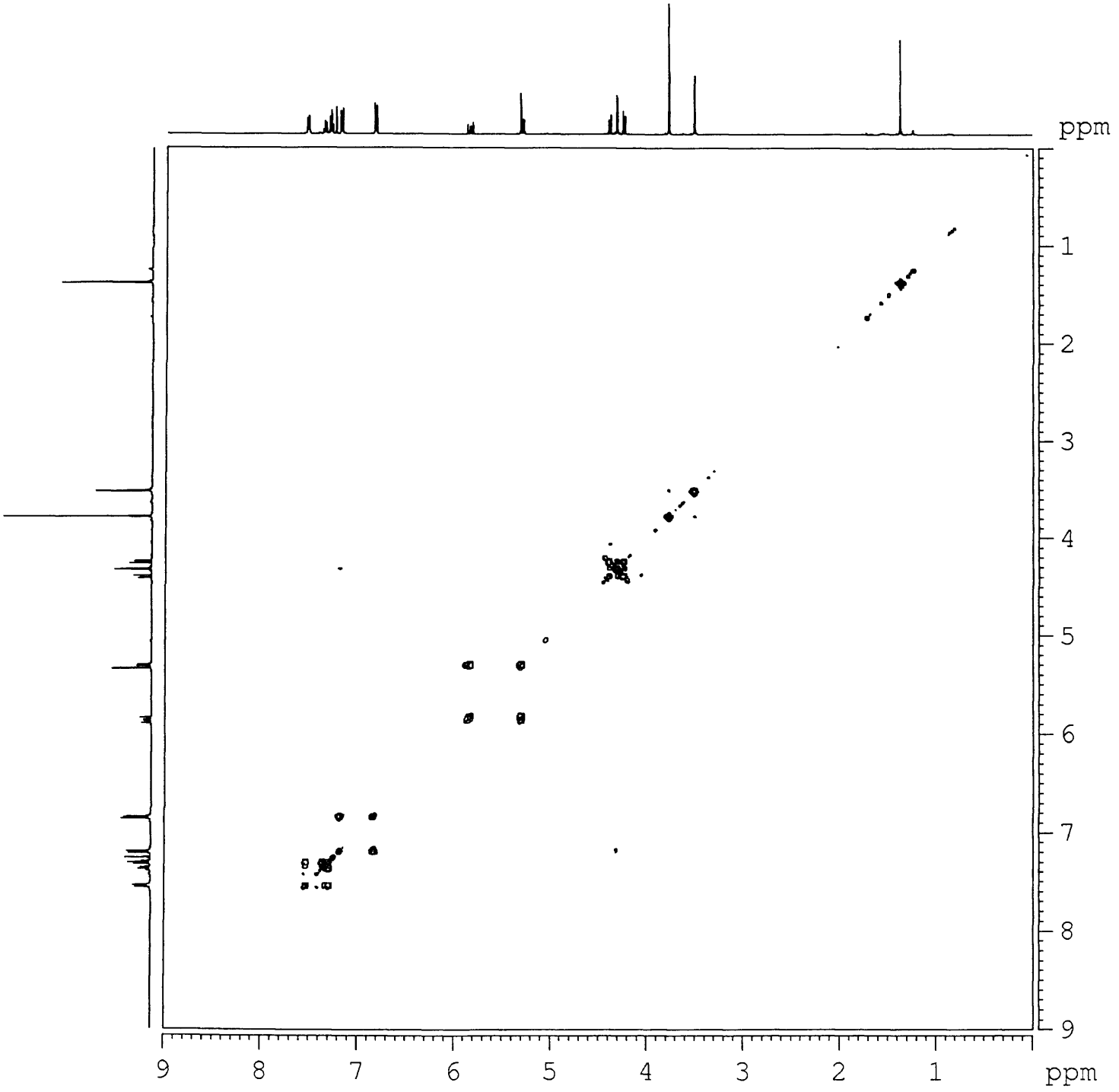
III-AL-163
dept
CDCl3 - 298K



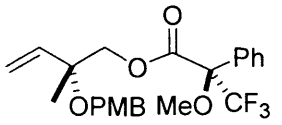


III-AL-163
13C
CDCl3 - 298K

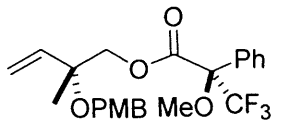


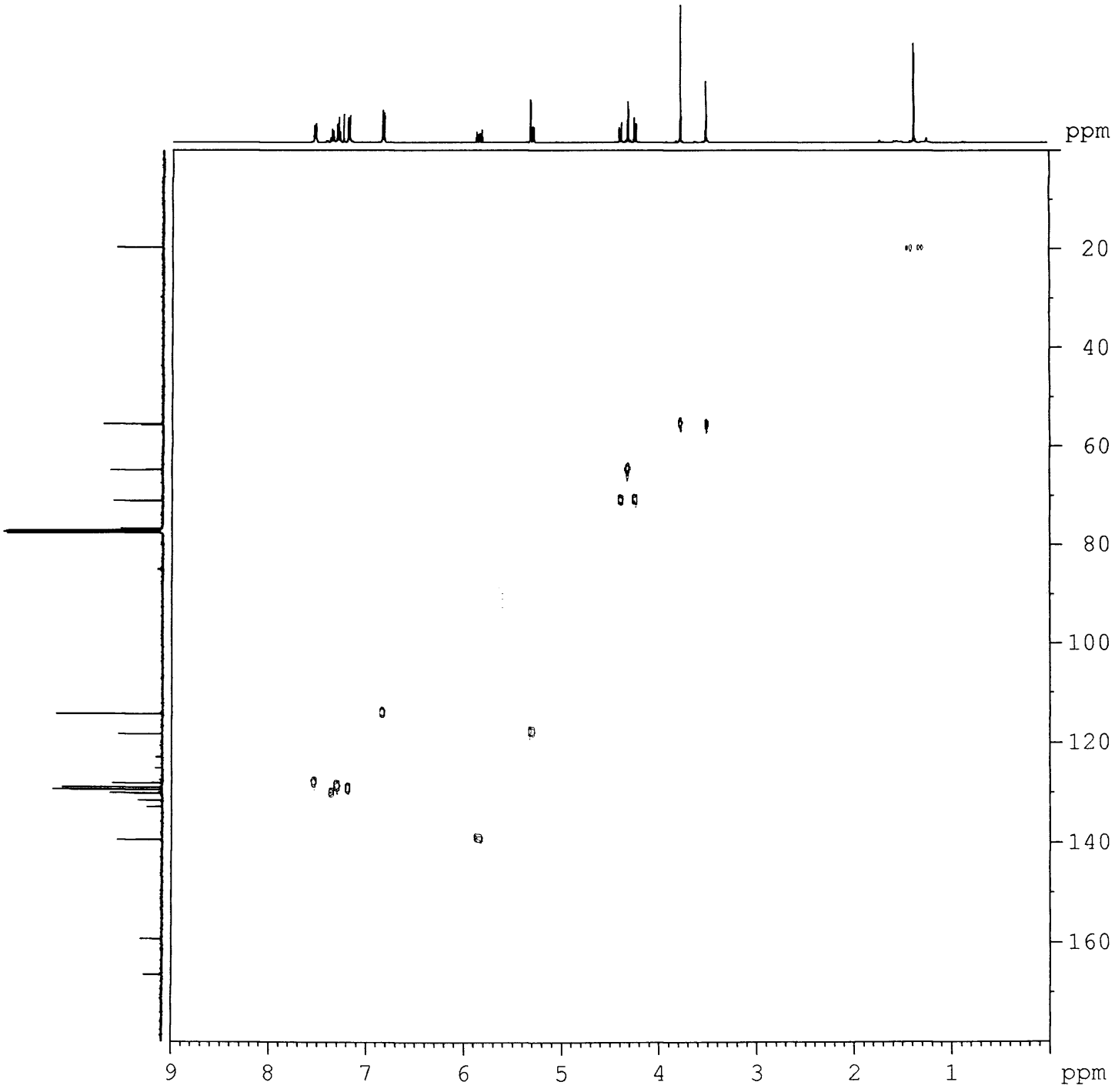


III-AL-163
cosy
CDCl3 - 298K

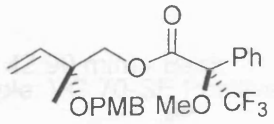


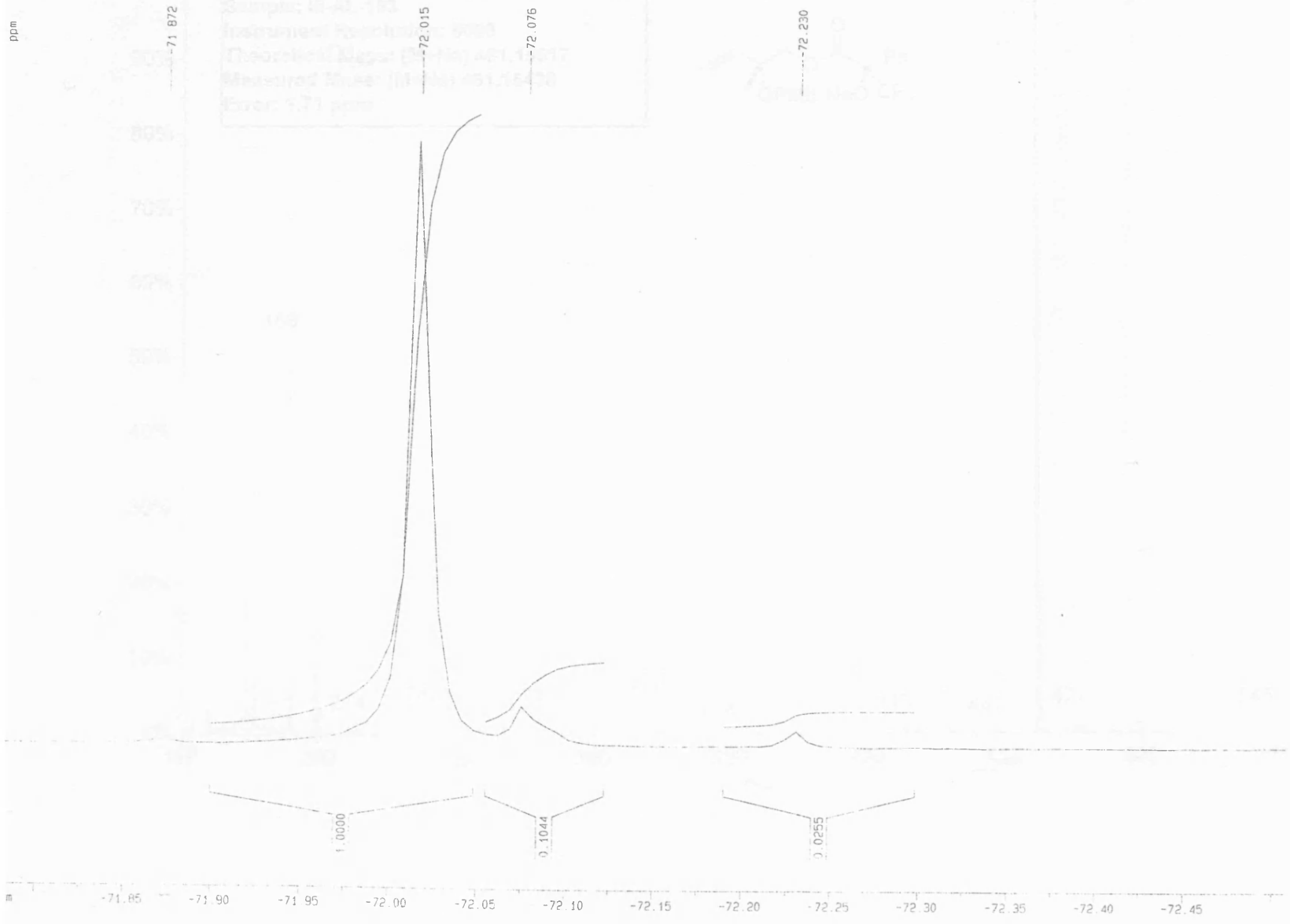
III-AL-163
HMQC
CDCl3 - 298K

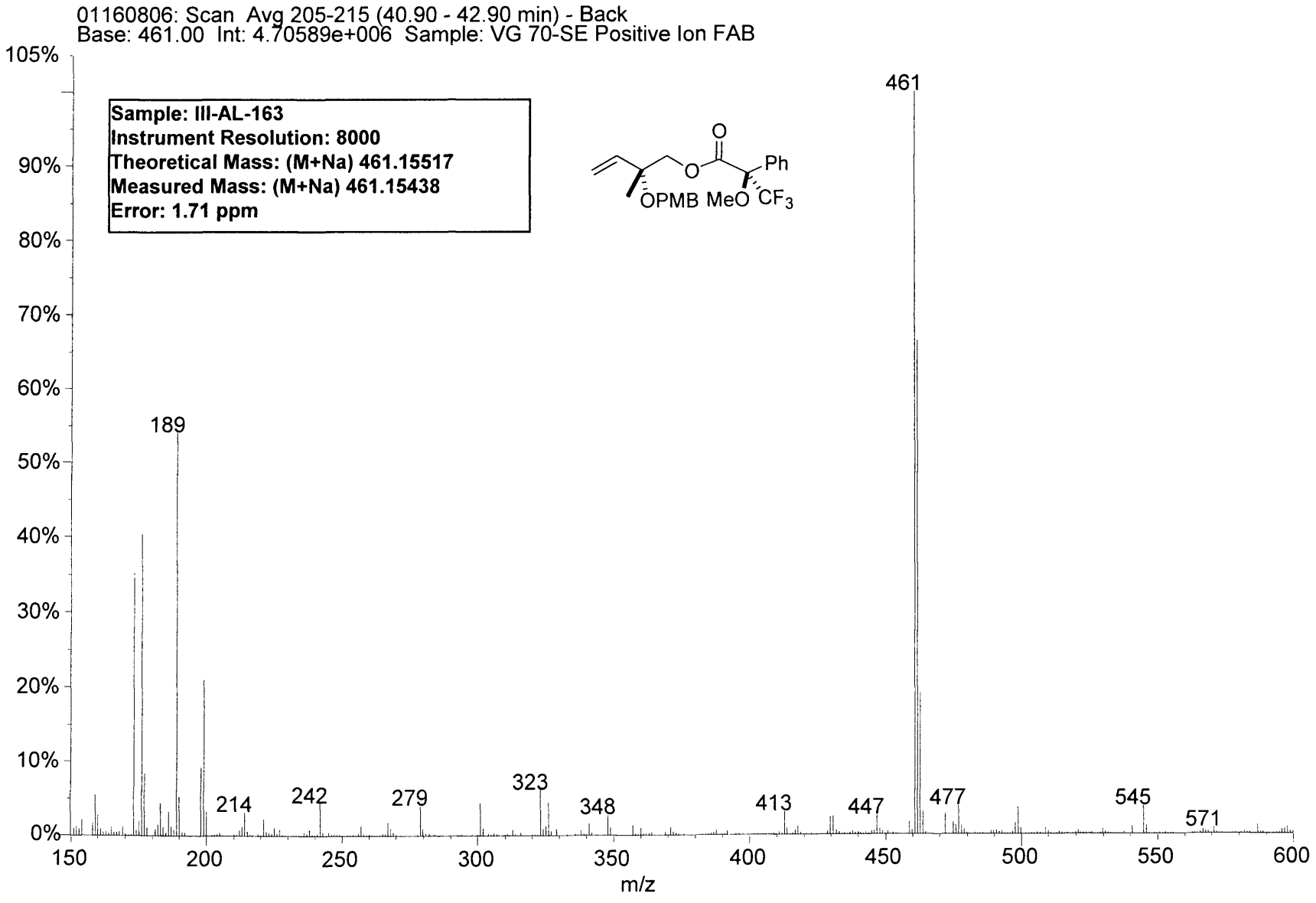


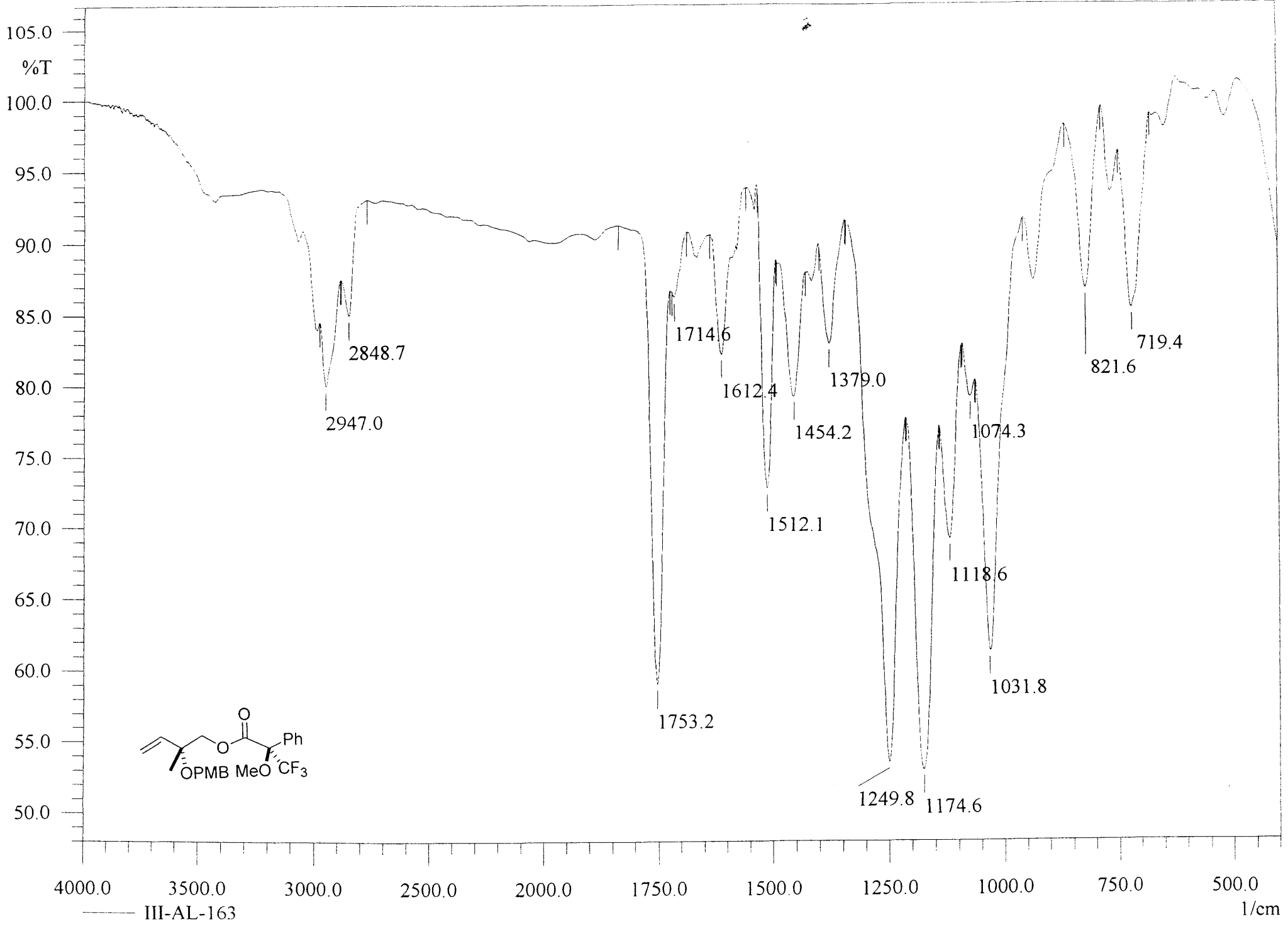


f19cpd.

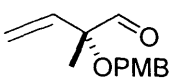

O
Ph
O
OPMB MeO CF3

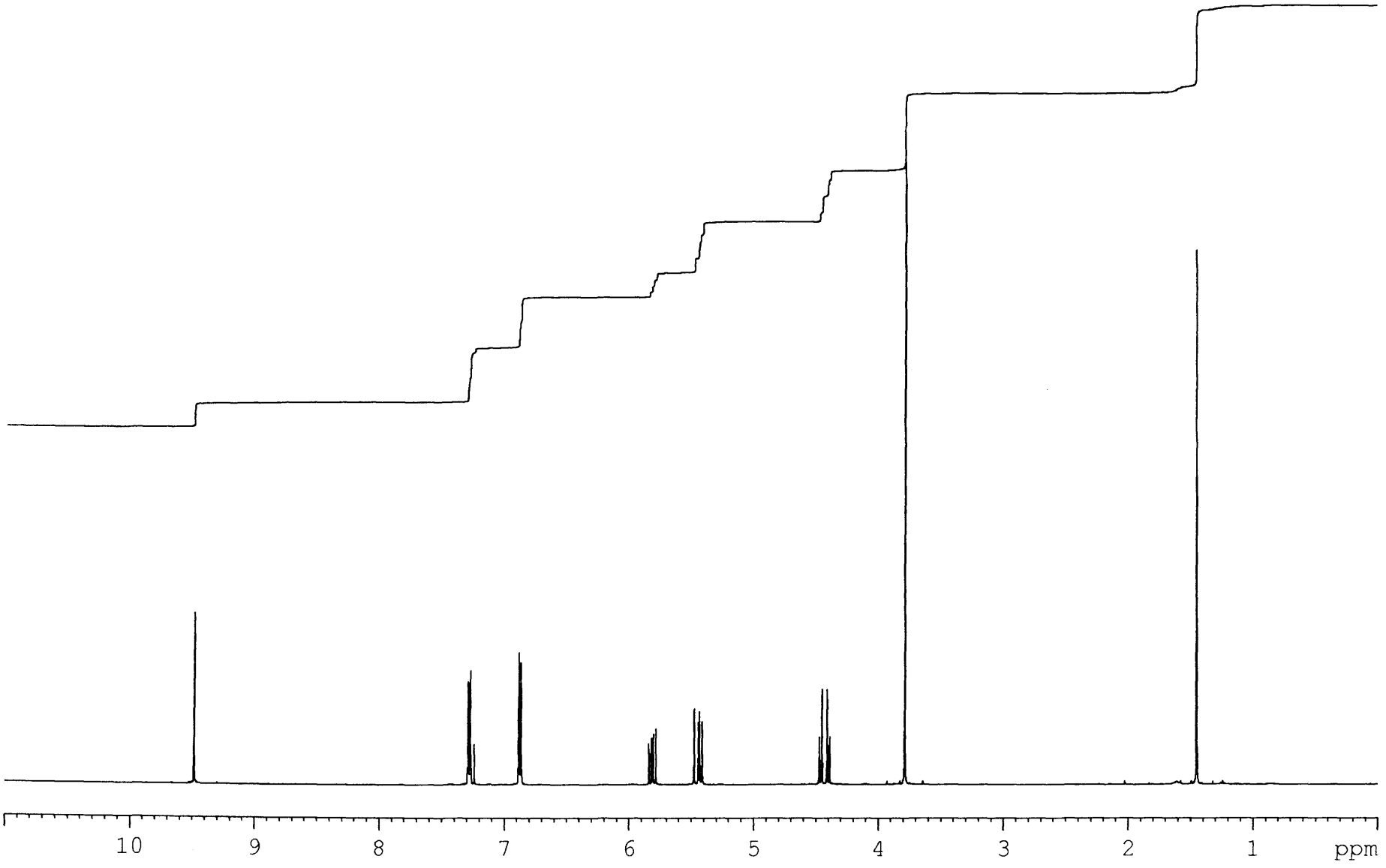

ppm
-71.872
-72.015
-72.076
-72.230
1.0000
0.1044
0.0255
-71.85
-71.90
-71.95
-72.00
-72.05
-72.10
-72.15
-72.20
-72.25
-72.30
-72.35
-72.40
-72.45


01160806: Scan Avg 205-215 (40.90 - 42.90 min) - Back
Base: 461.00 Int: 4.70589e+006 Sample: VG 70-SE Positive Ion FAB
Sample: III-AL-163
Instrument Resolution: 8000
Theoretical Mass: (M+Na) 461.15517
Measured Mass: (M+Na) 461.15438
Error: 1.71 ppm
OPMB MeO CF3
Ph
105%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
461
189
214
242
279
323
348
413
447
477
545
571
150
200
250
300
350
400
450
500
550
600
m/z

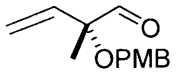

105.0
%T
100.0
95.0
90.0
85.0
80.0
75.0
70.0
65.0
60.0
55.0
50.0
2848.7
2947.0
1714.6
1612.4
1379.0
1454.2
1074.3
1512.1
1118.6
1031.8
1753.2
1249.8
1174.6
821.6
719.4
O
O
Ph
OPMB MeO CF3
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
III-AL-163

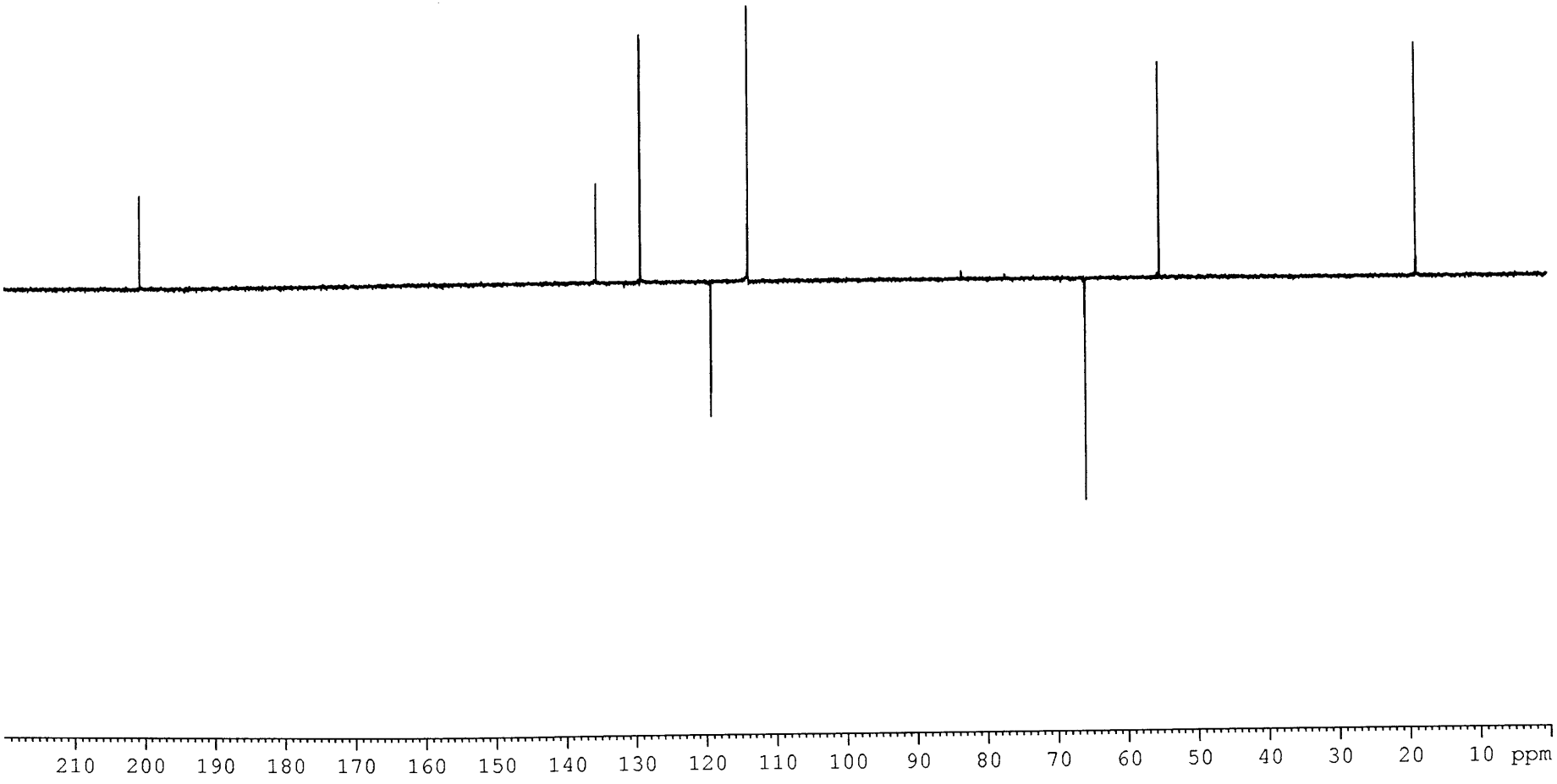
IV-AL-13
CDCl3 - 298K



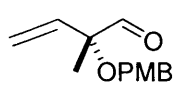


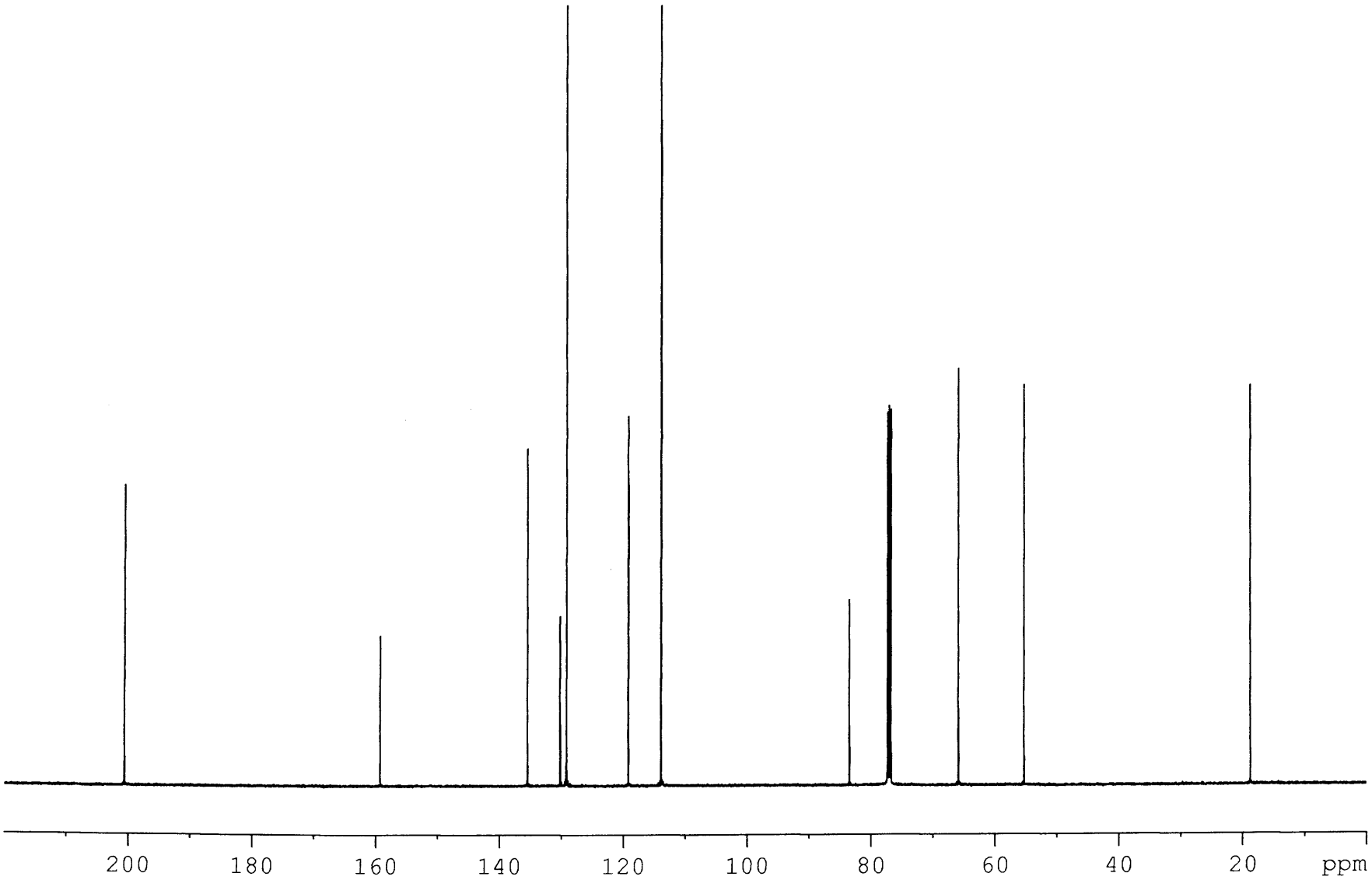
IV-AL-13
dept
CDCl3 - 298K

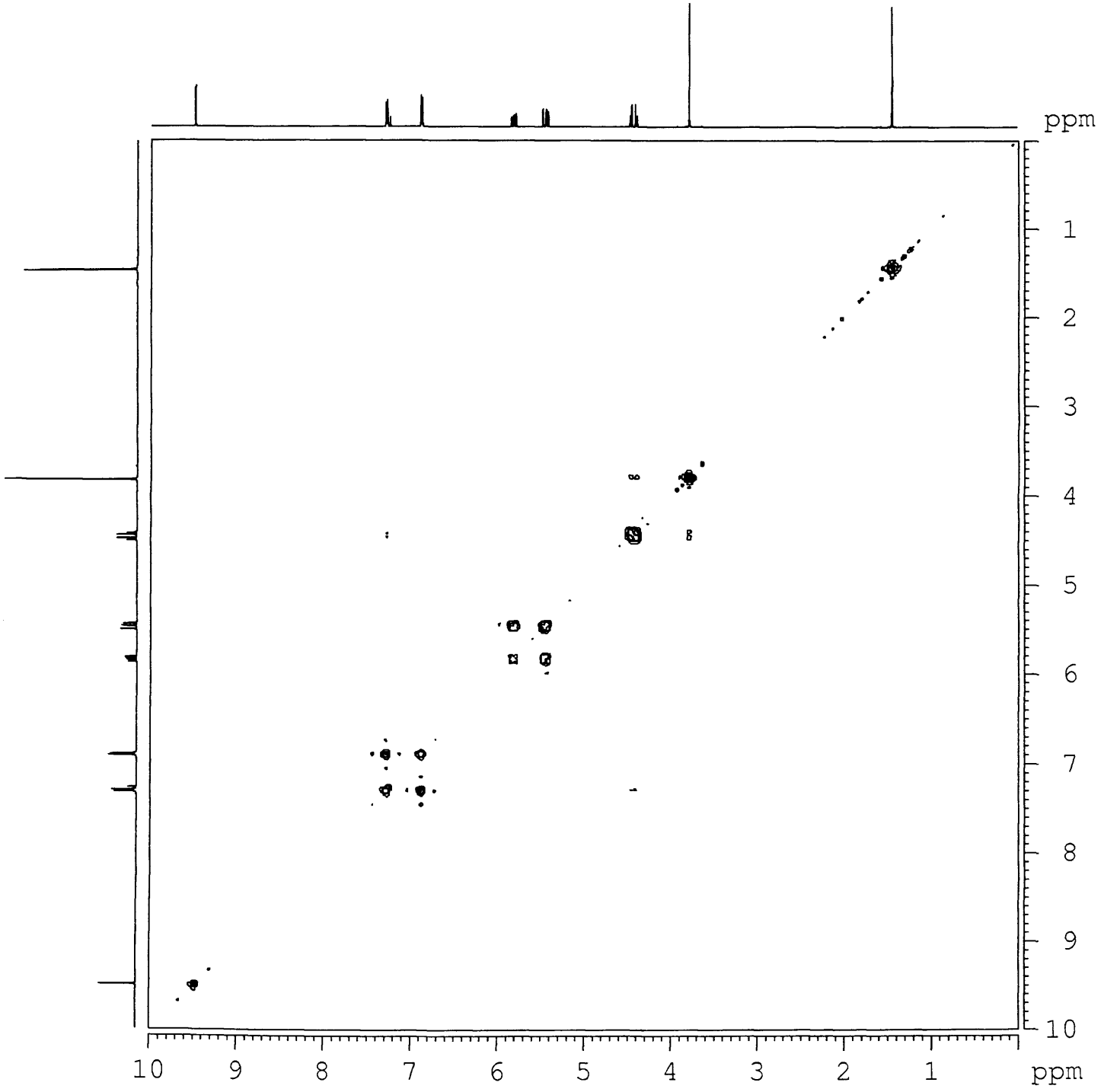




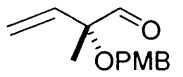
IV-AL-13
13C
CDCl3 - 298K



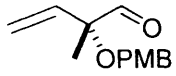


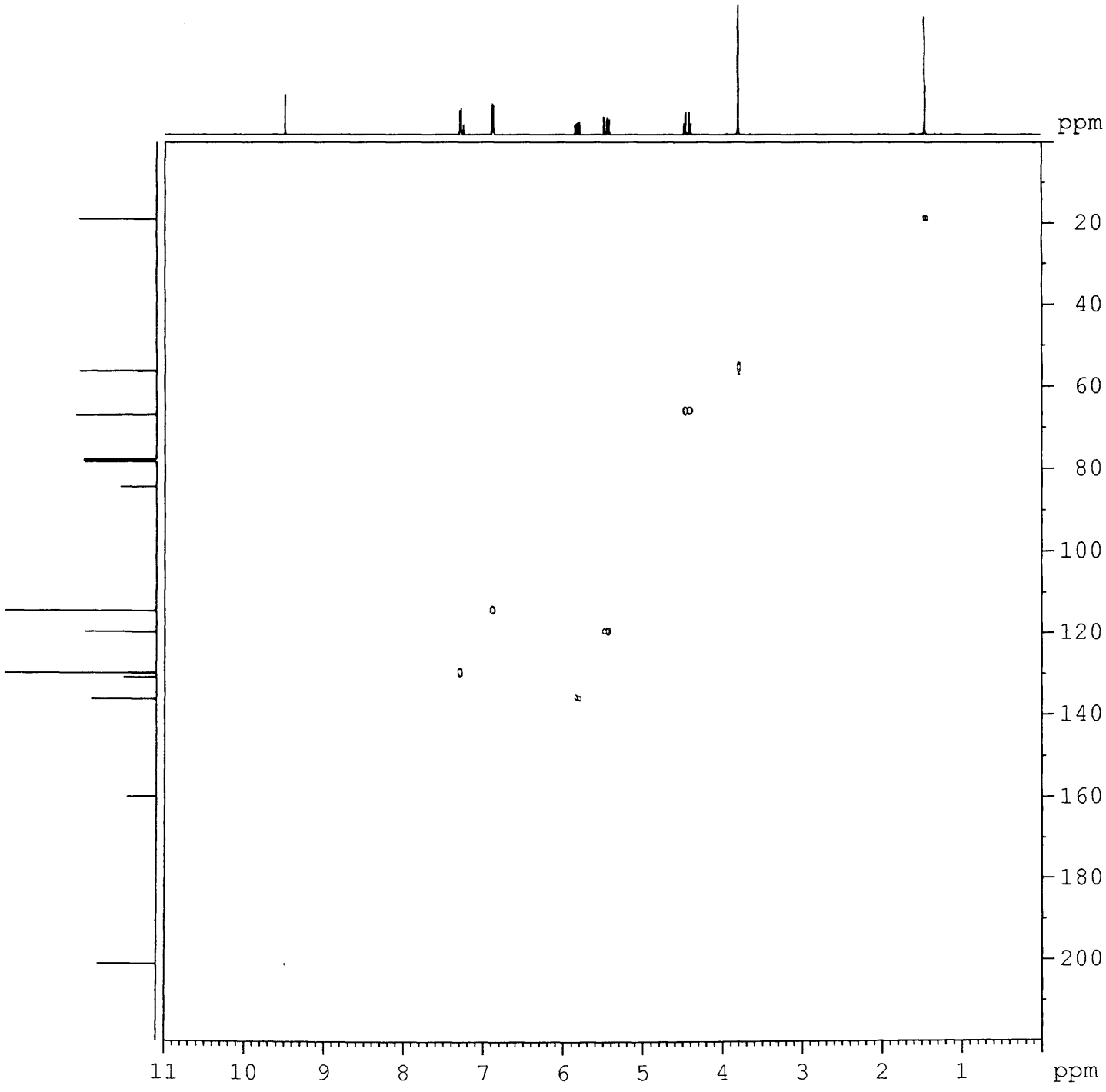


IV-AL-13
COSY
CDCl3 - 298K

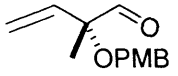


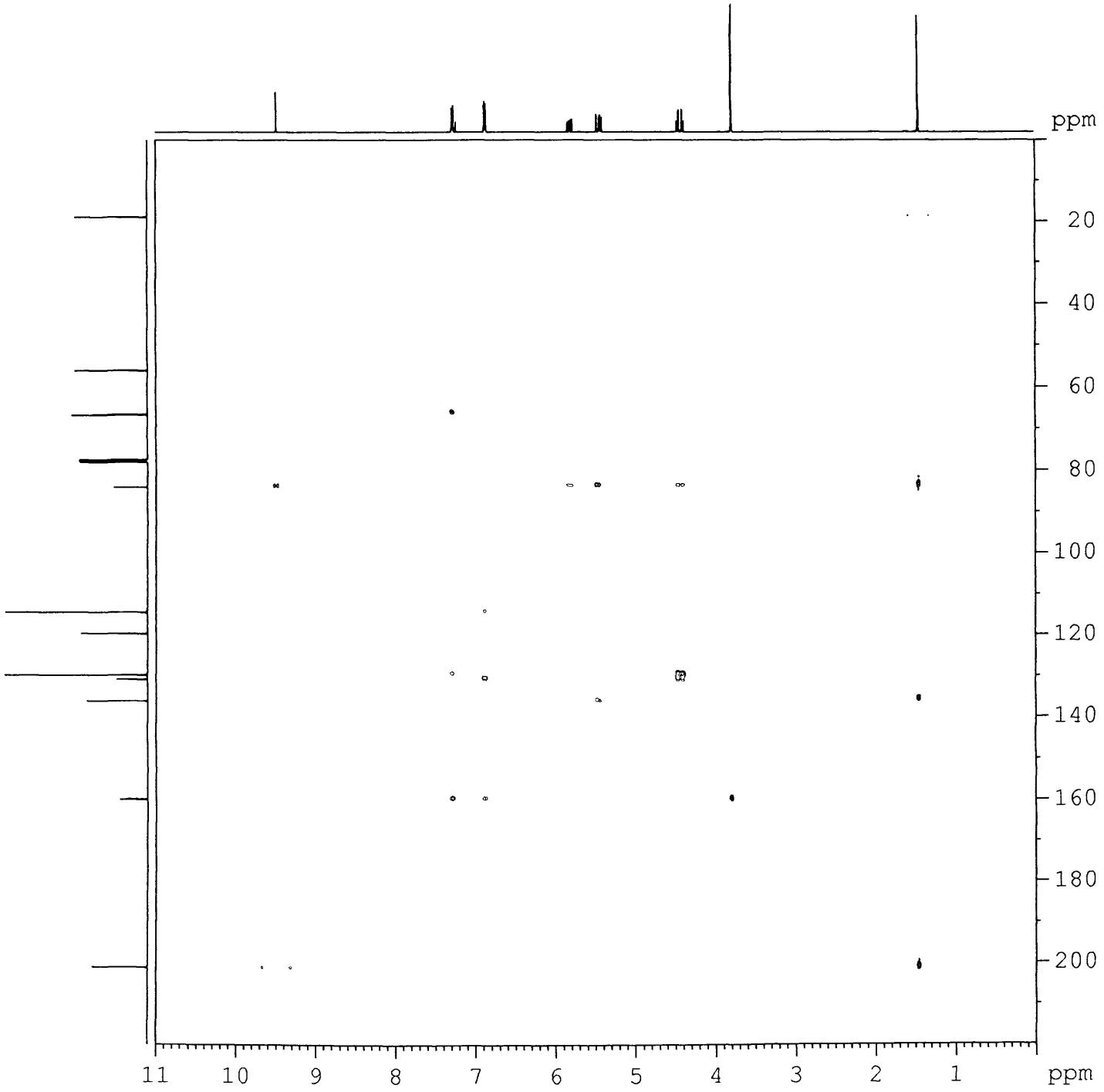
IV-AL-13
HMQC
CDCl3 - 293K

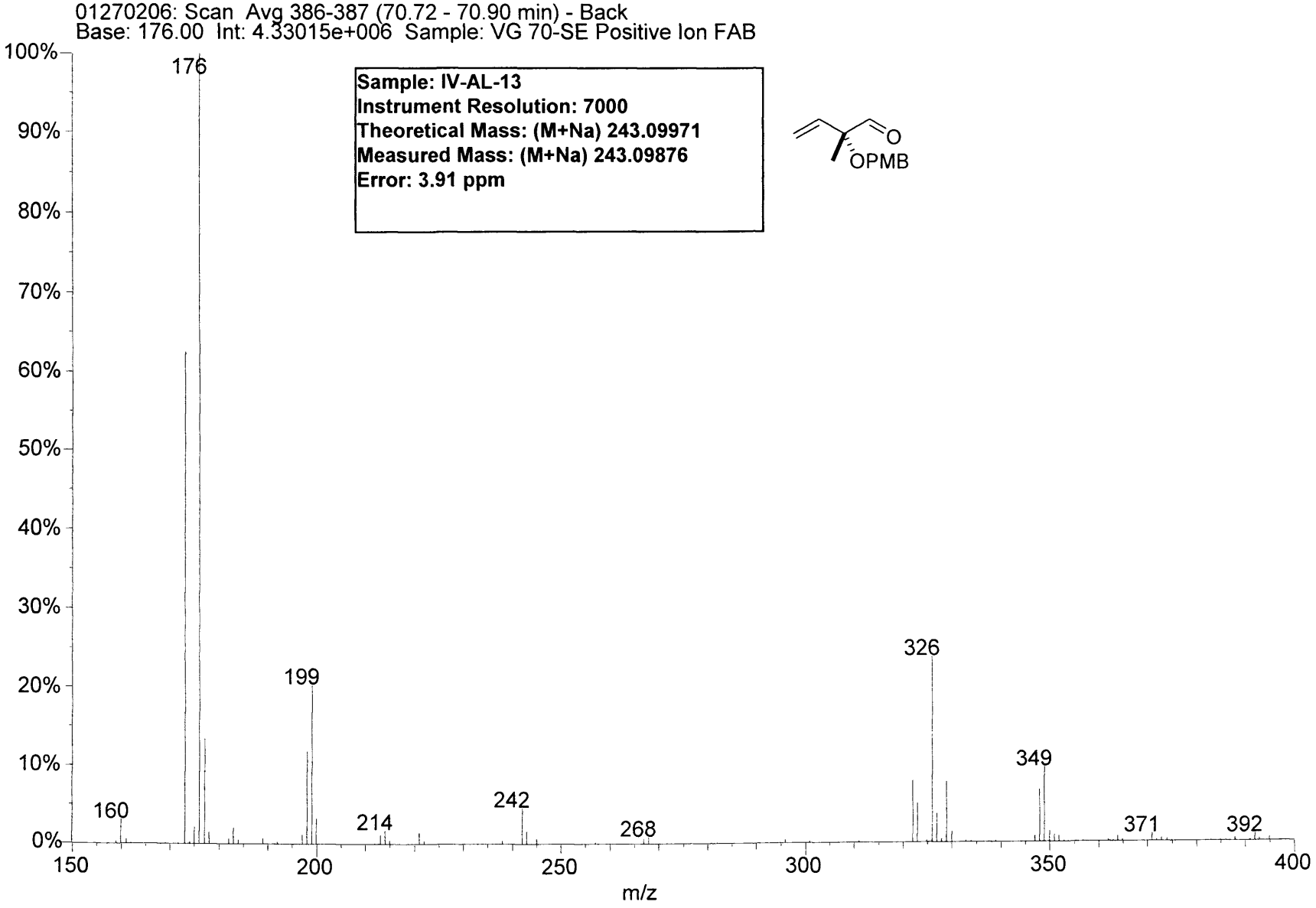


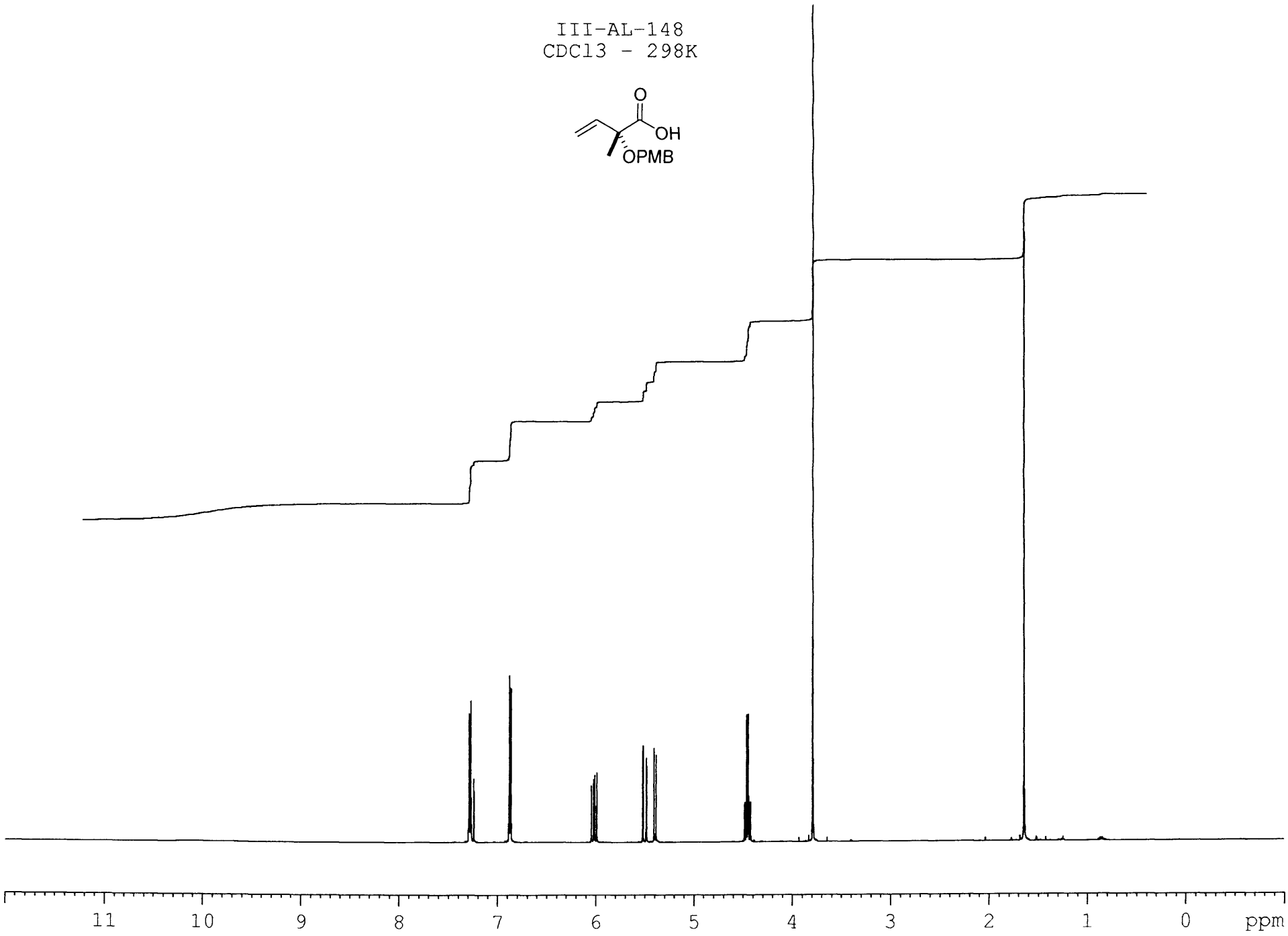


IV-AL-13
HMBC
CDCl3 - 298K

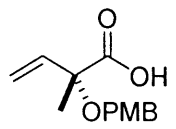




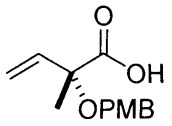

01270206: Scan Avg 386-387 (70.72 - 70.90 min) - Back
Base: 176.00 Int: 4.33015e+006 Sample: VG 70-SE Positive Ion FAB
Sample: IV-AL-13
Instrument Resolution: 7000
Theoretical Mass: (M+Na) 243.09971
Measured Mass: (M+Na) 243.09876
Error: 3.91 ppm
O
OPMB
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
176
199
326
349
160
214
242
268
371
392
150
200
250
300
350
400
m/z

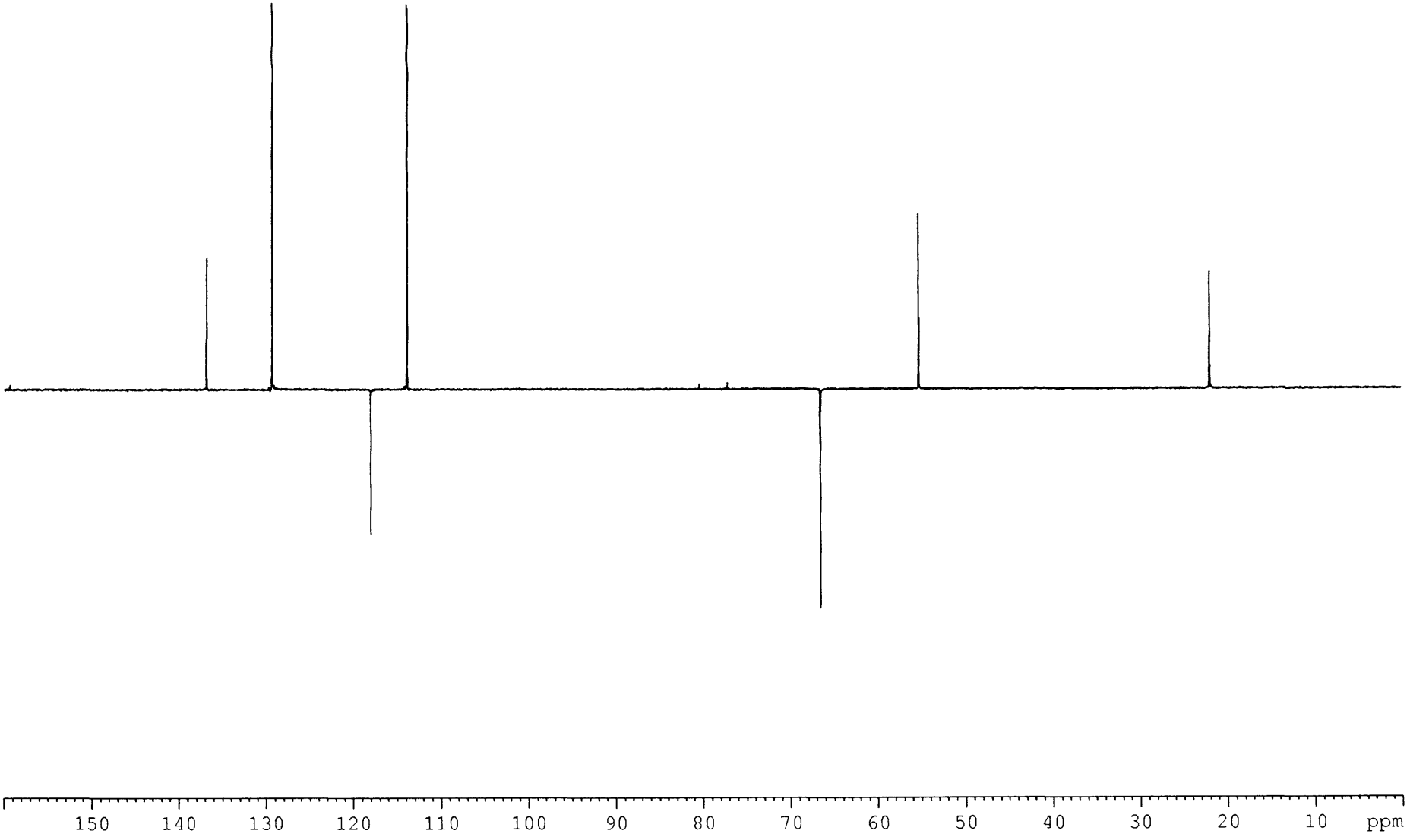

III-AL-148
CDCl3 - 298K
O
OH
OPMB
11
10
9
8
7
6
5
4
3
2
1
0
ppm

III-AL-148
CDCl3 - 298K

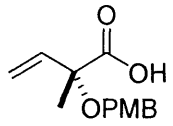


III-AL-148
DEPT
CDCl3 - 298K

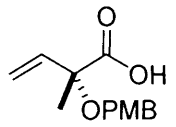


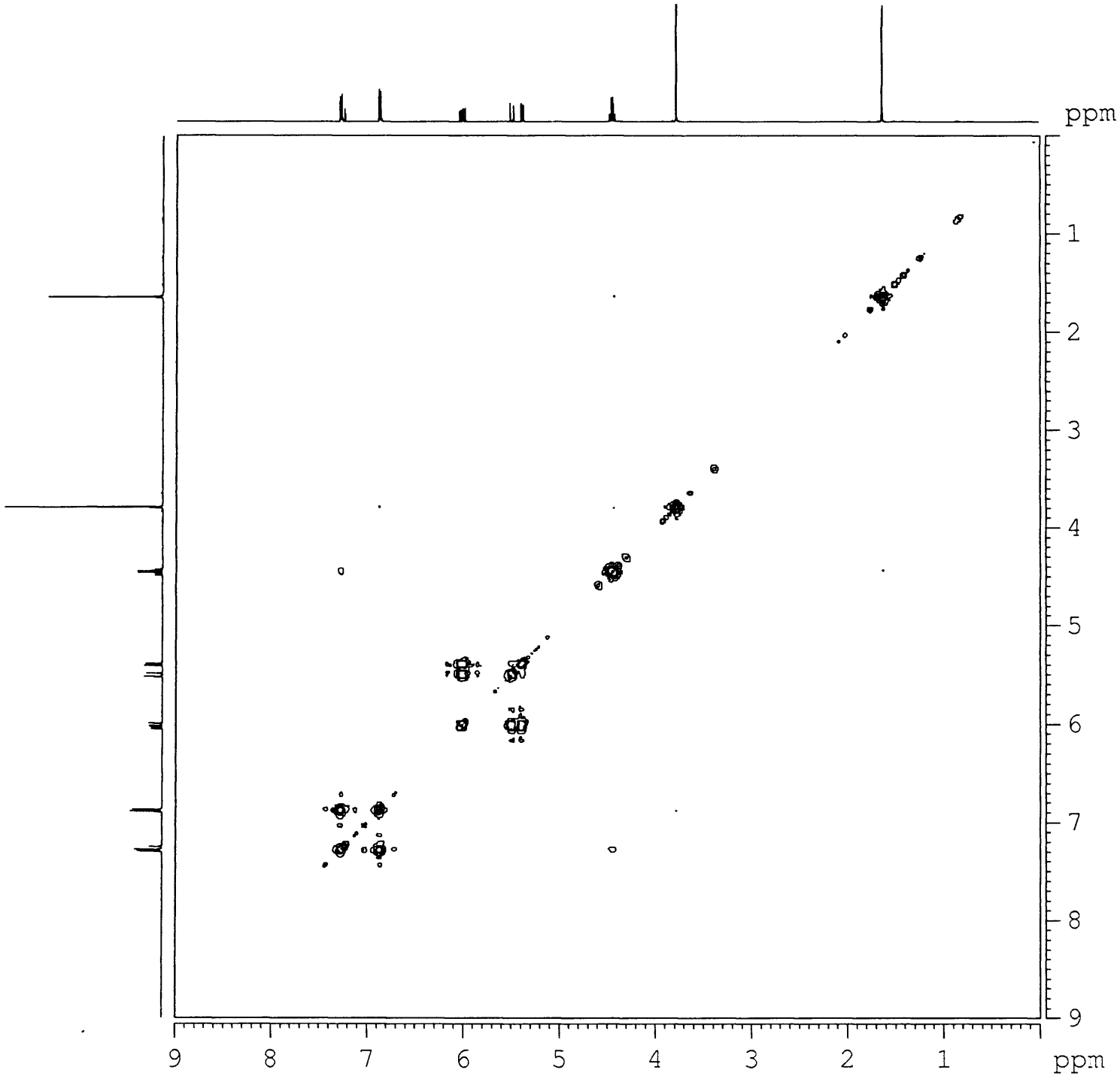


III-AL-148
13C
CDCl3 - 298K

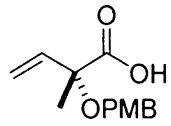


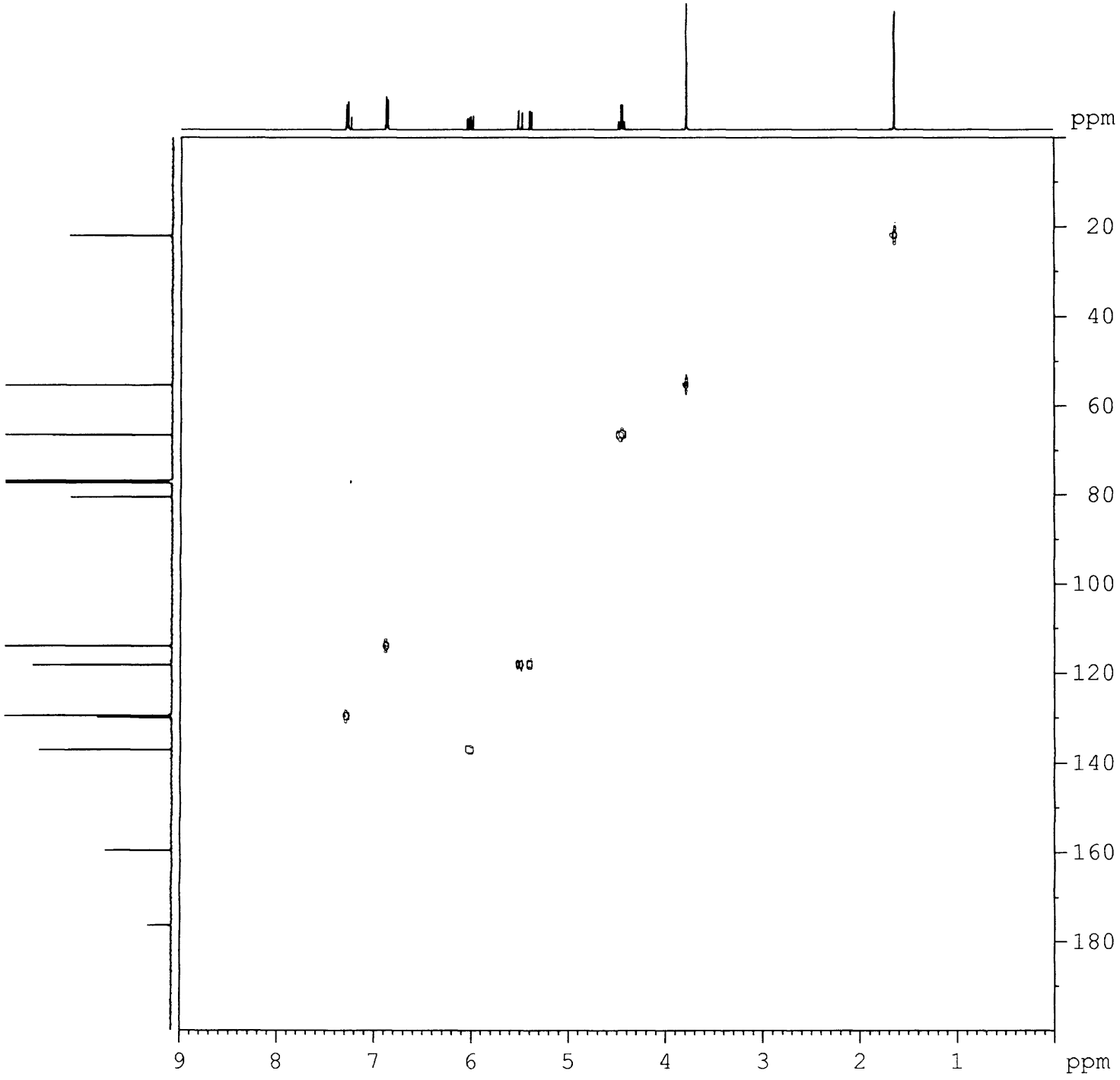
III-AL-148
COSY
CDCl3 - 298K

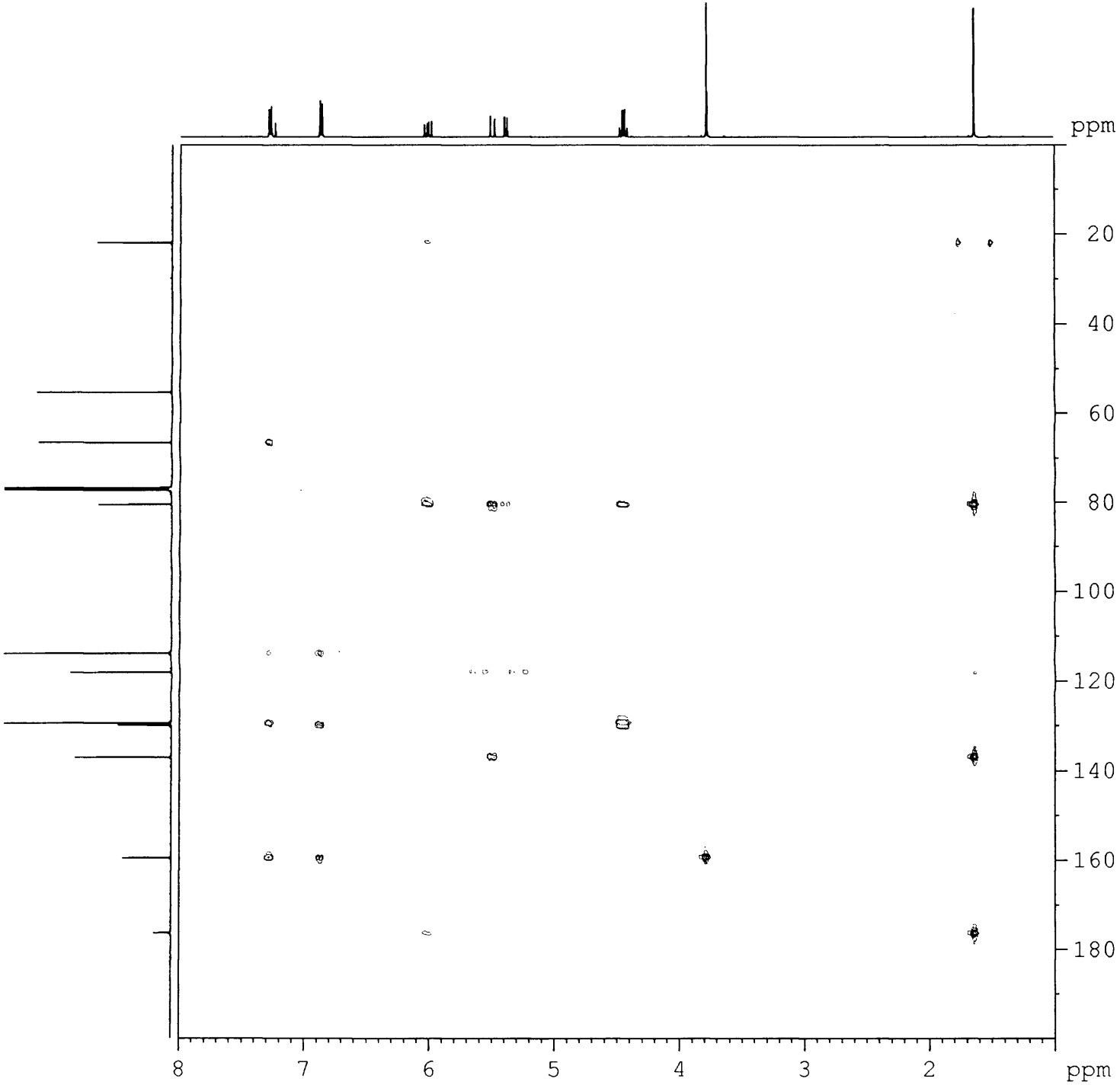




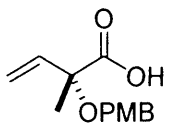
III-AL-148
HMQC
CDCl3 - 298K

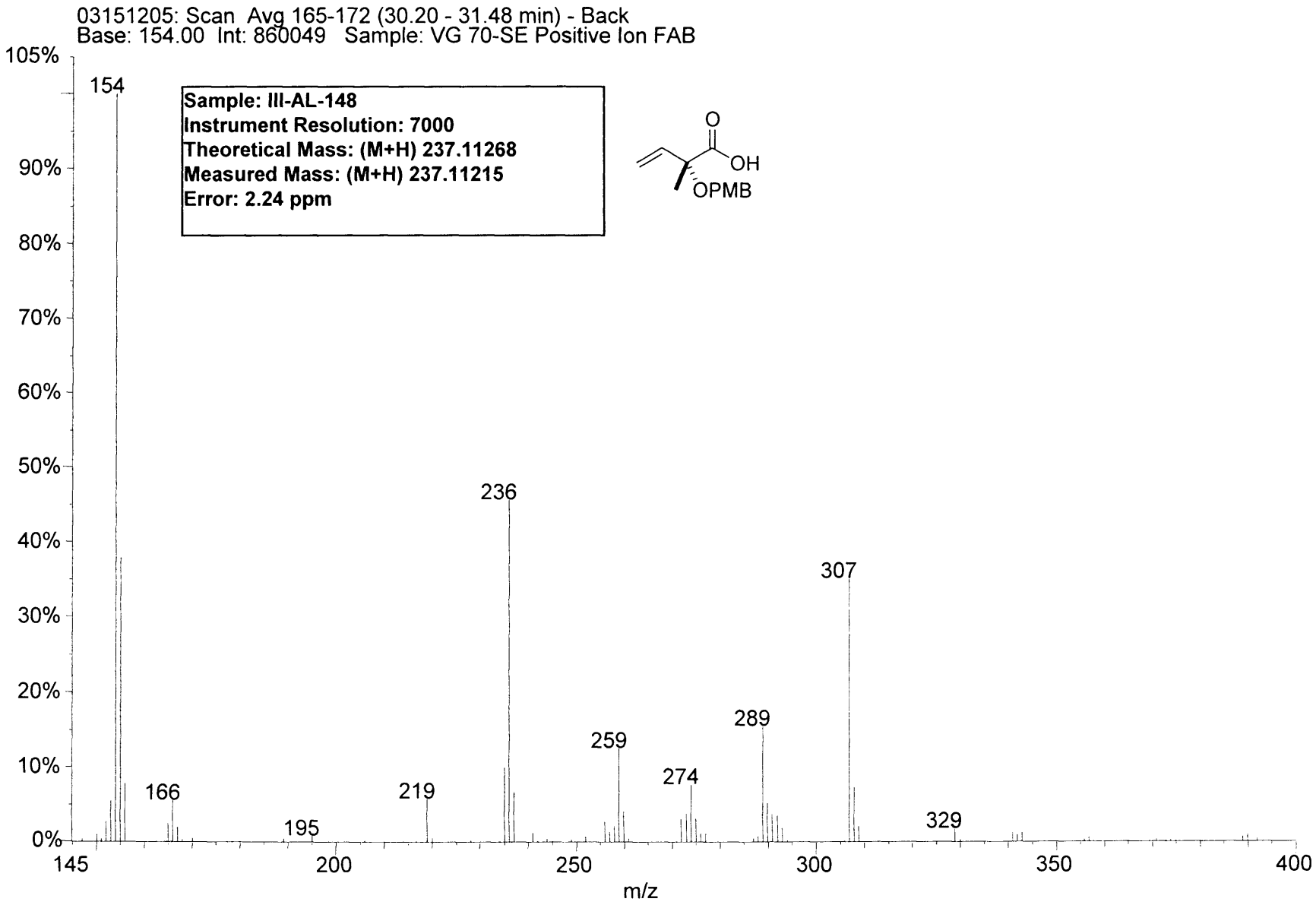


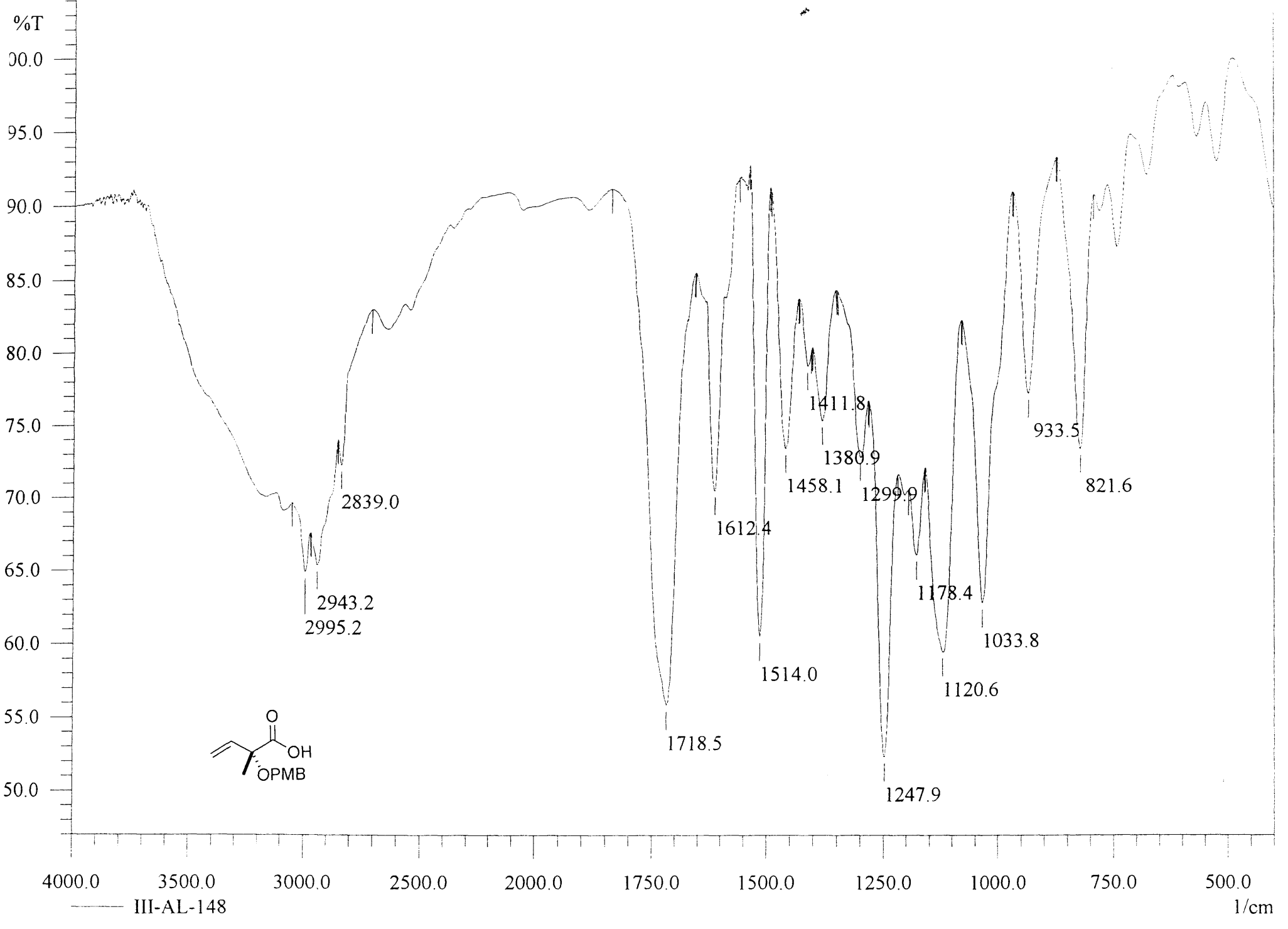




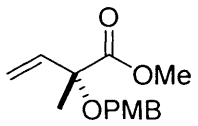
III-AL-148
HMBC
CDCl3 - 298K



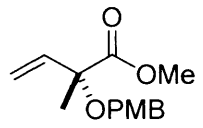

03151205: Scan Avg 165-172 (30.20 - 31.48 min) - Back
Base: 154.00 Int: 860049 Sample: VG 70-SE Positive Ion FAB
Sample: III-AL-148
Instrument Resolution: 7000
Theoretical Mass: (M+H) 237.11268
Measured Mass: (M+H) 237.11215
Error: 2.24 ppm
O
OH
OPMB
105%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
154
166
195
219
236
259
274
289
307
329
145
200
250
300
350
400
m/z

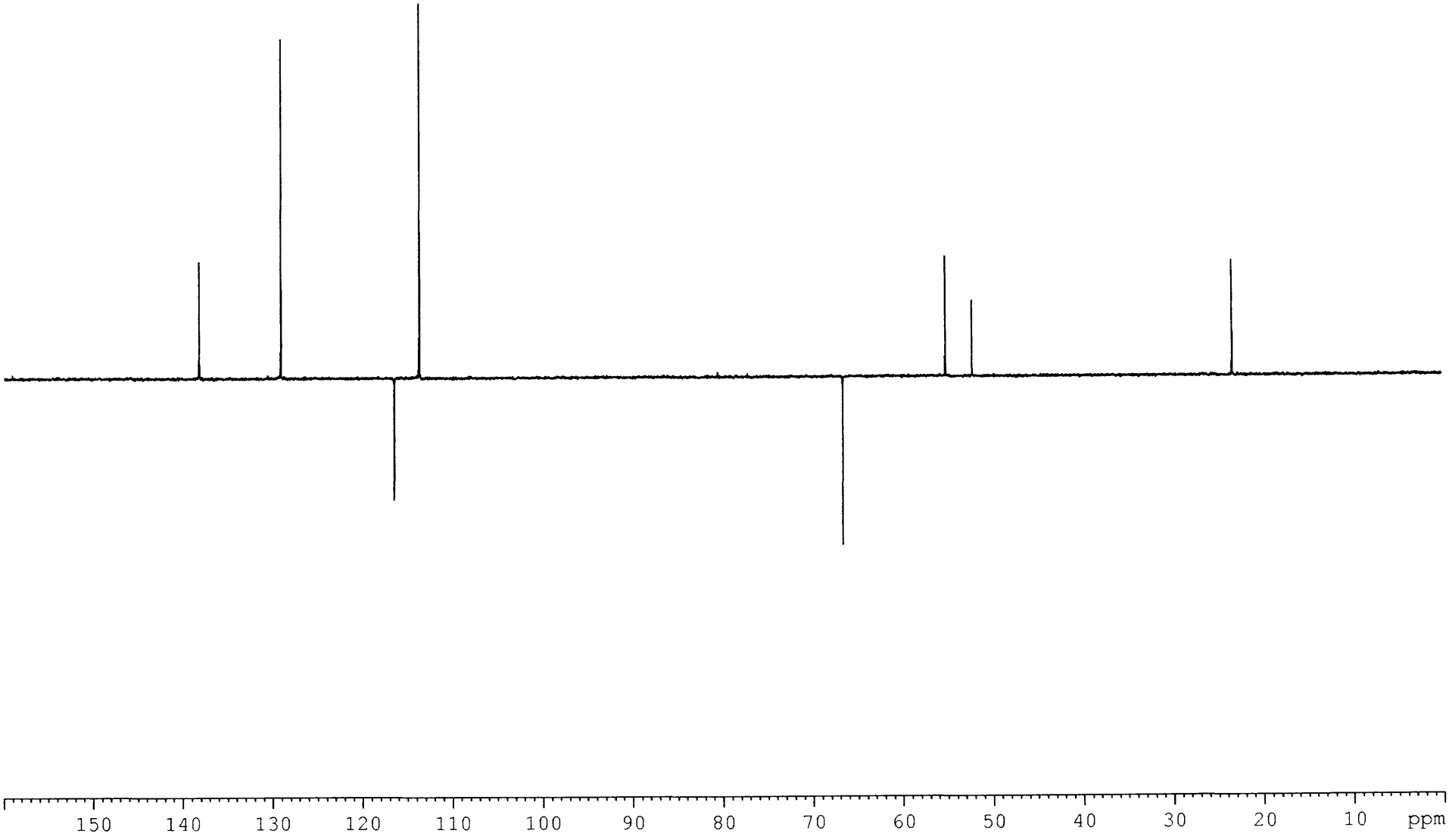

%T
100.0
95.0
90.0
85.0
80.0
75.0
70.0
65.0
60.0
55.0
50.0
2839.0
2943.2
2995.2
1612.4
1718.5
1514.0
1458.1
1411.8
1380.9
1299.9
1247.9
1178.4
1120.6
1033.8
933.5
821.6
O
OH
OPMB
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
III-AL-148
1/cm

III-AL-149
CDCl3 - 298K

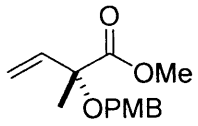


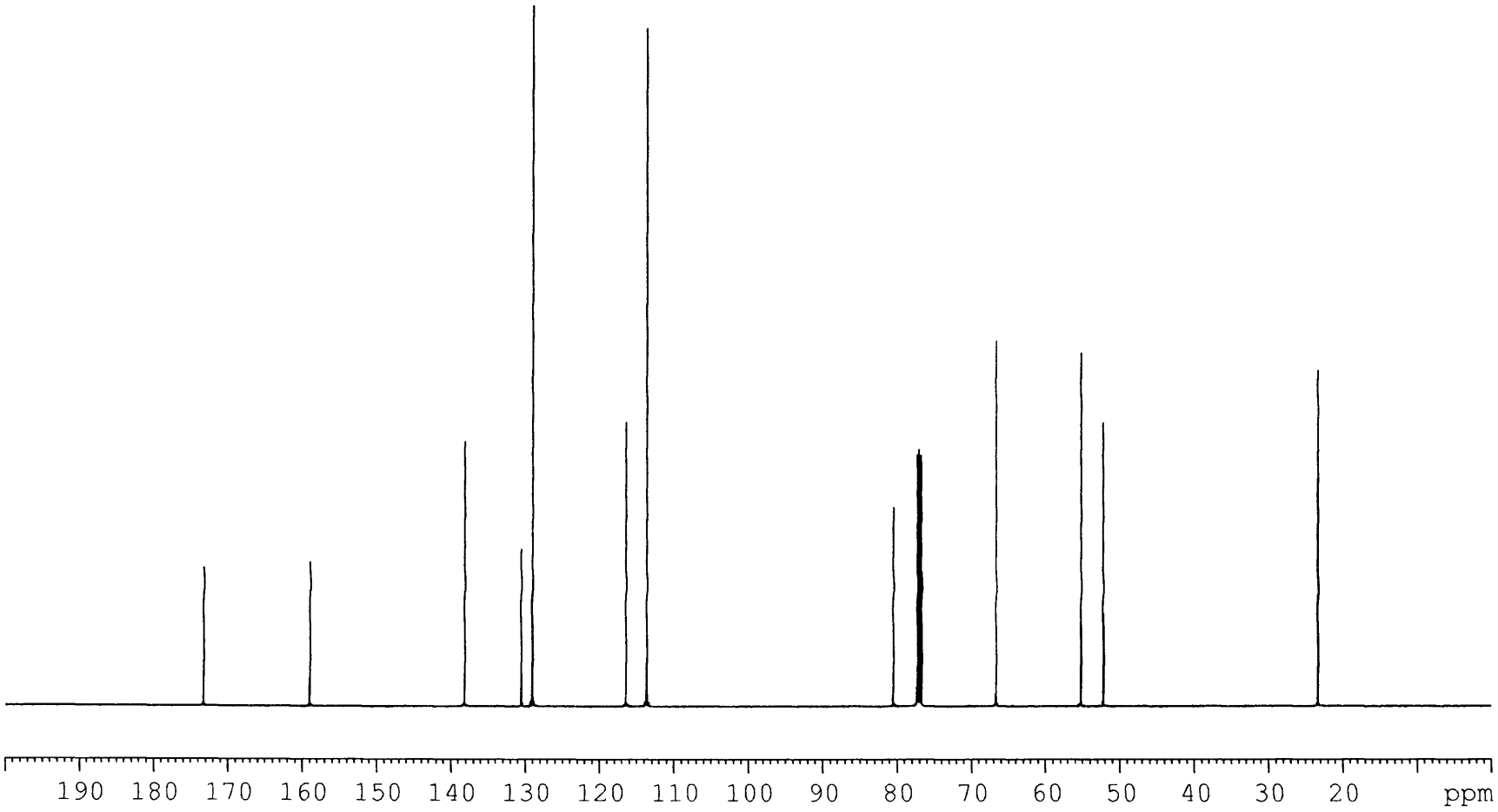
III-AL-149
DEPT
CDCl3 - 298K



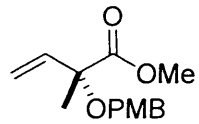


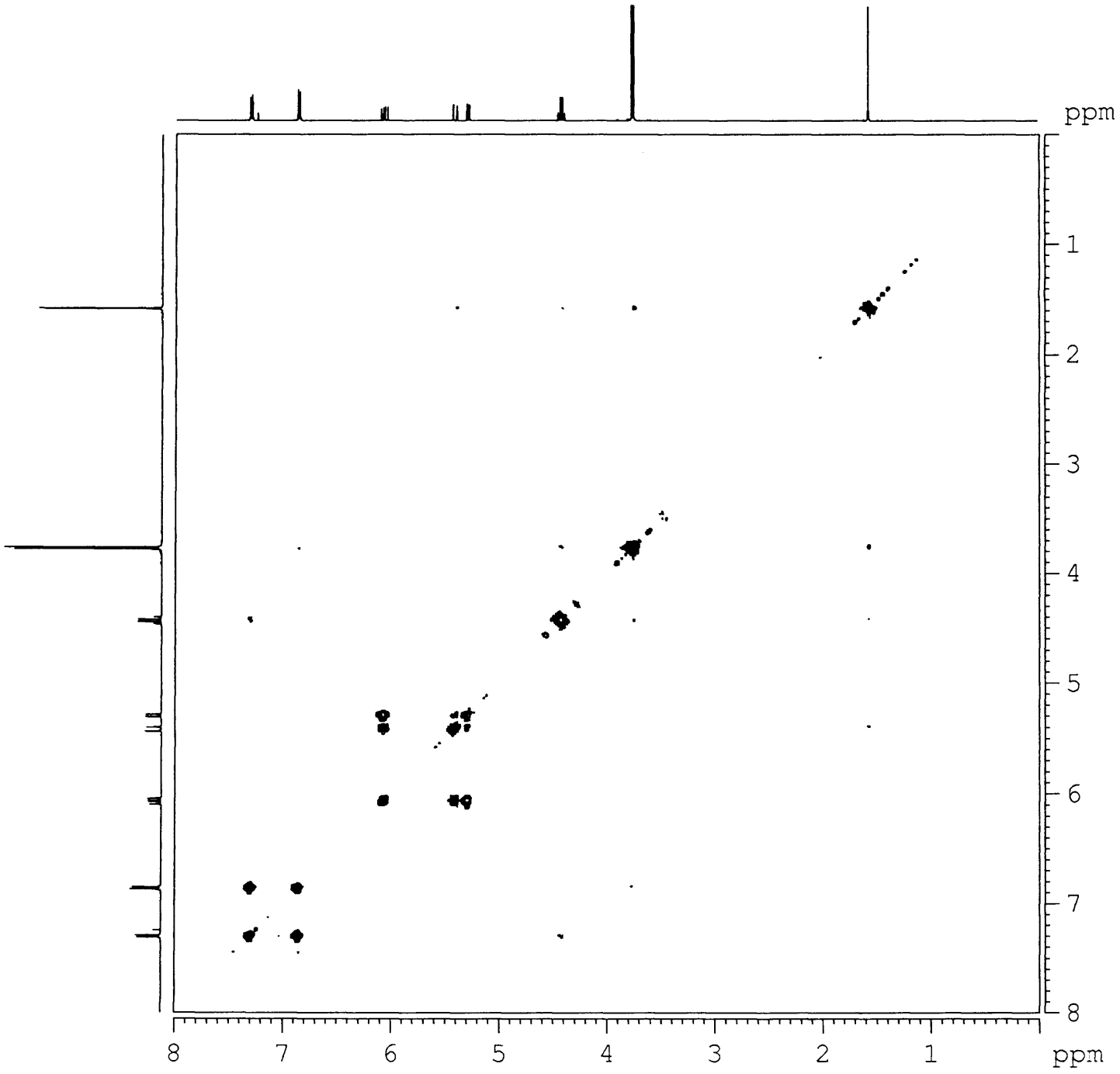
III-AL-149
13C
CDCl3 - 298K



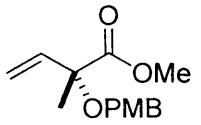


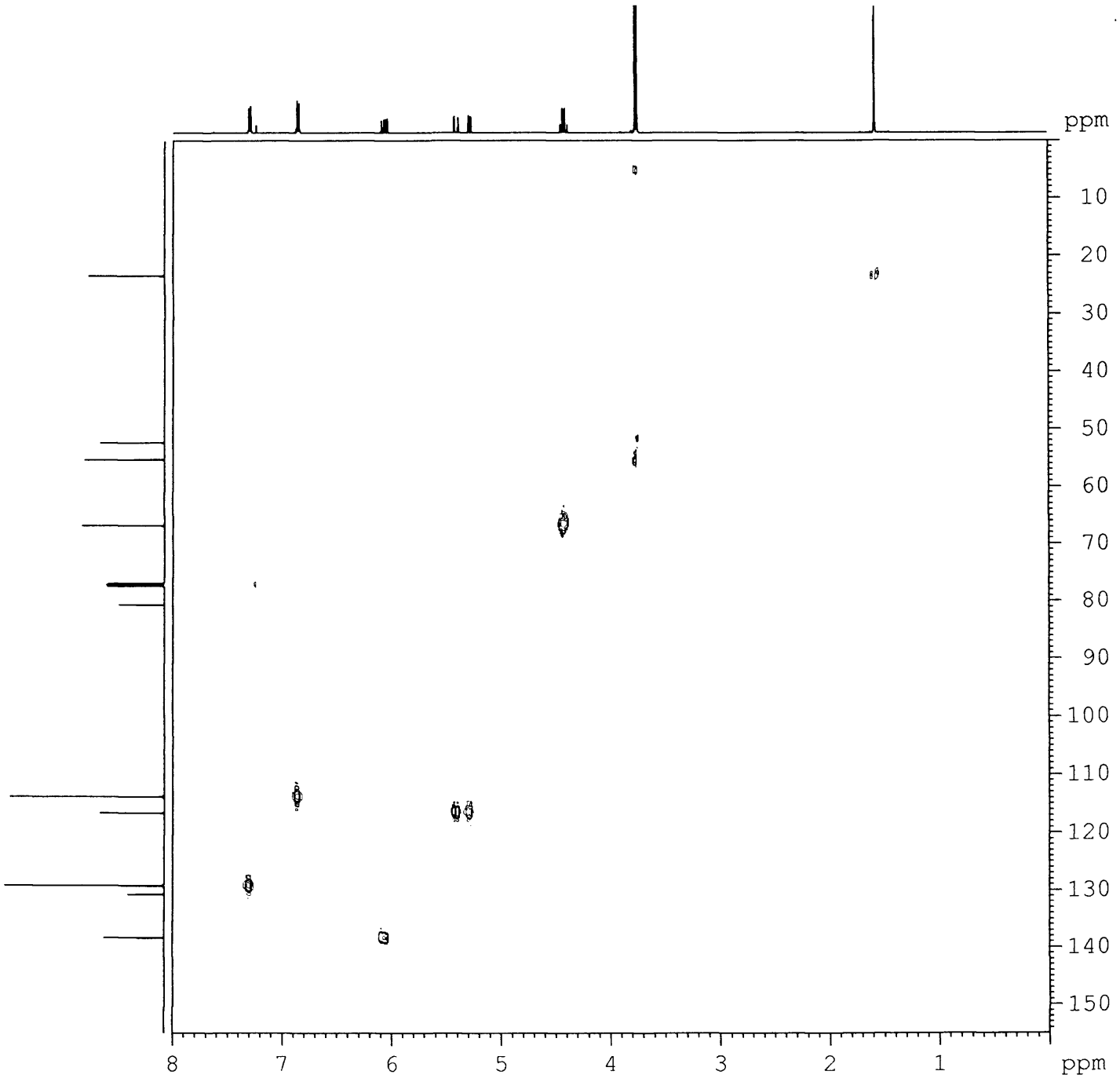
III-AL-149
COSY
CDCl3 - 298K



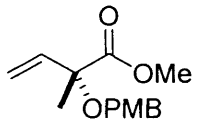


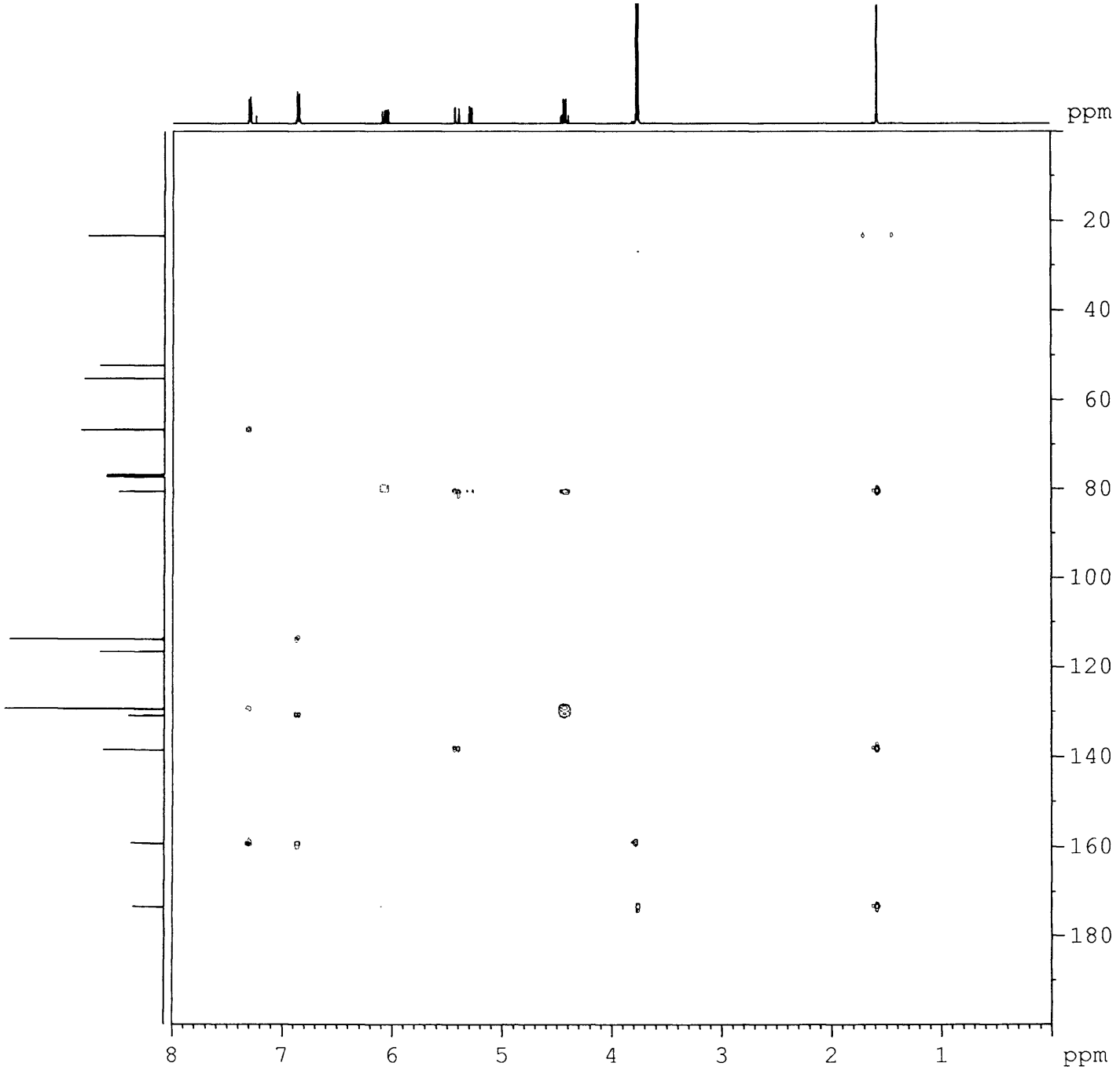
III-AL-149
HMQC
CDCl3 - 298K

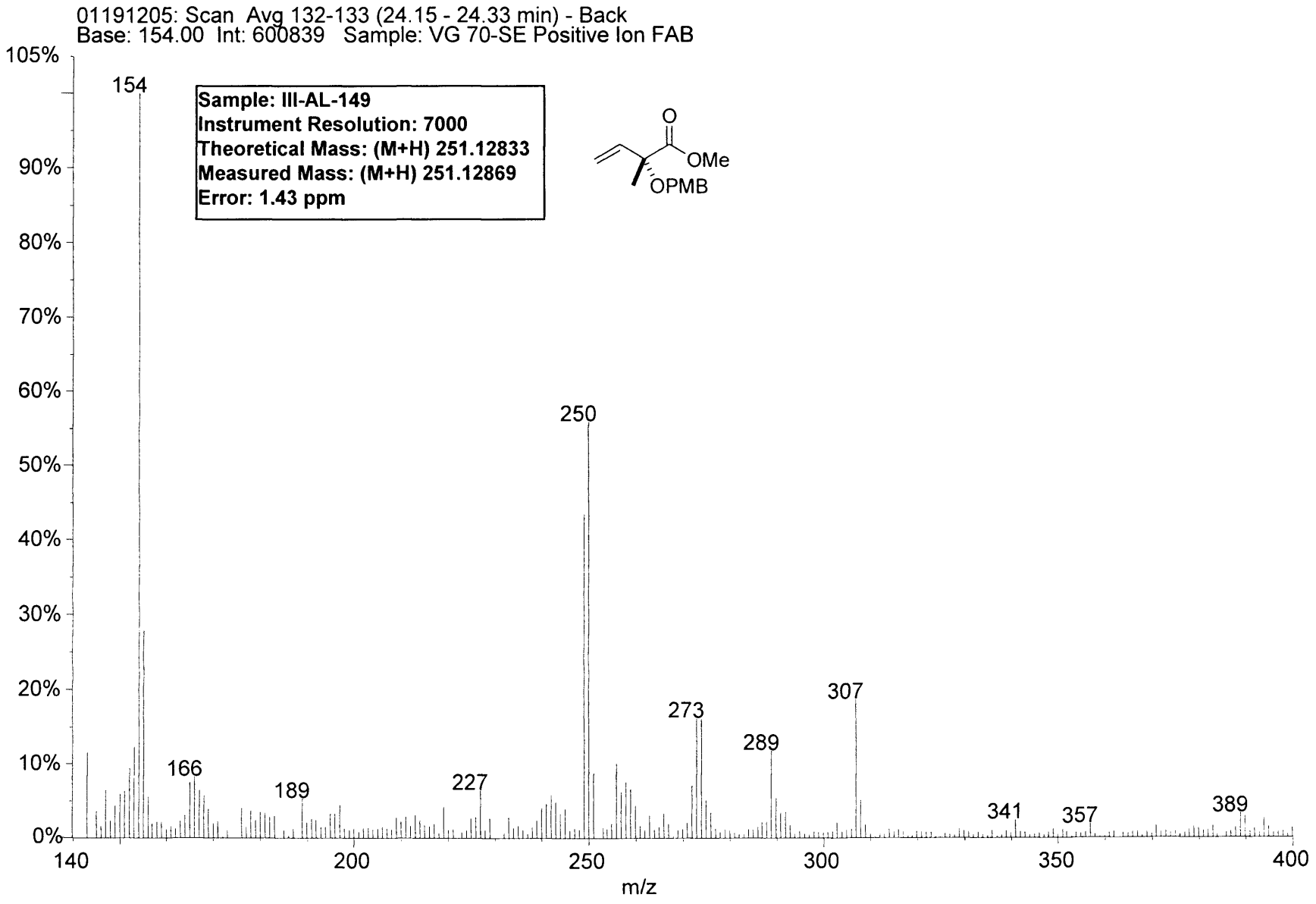


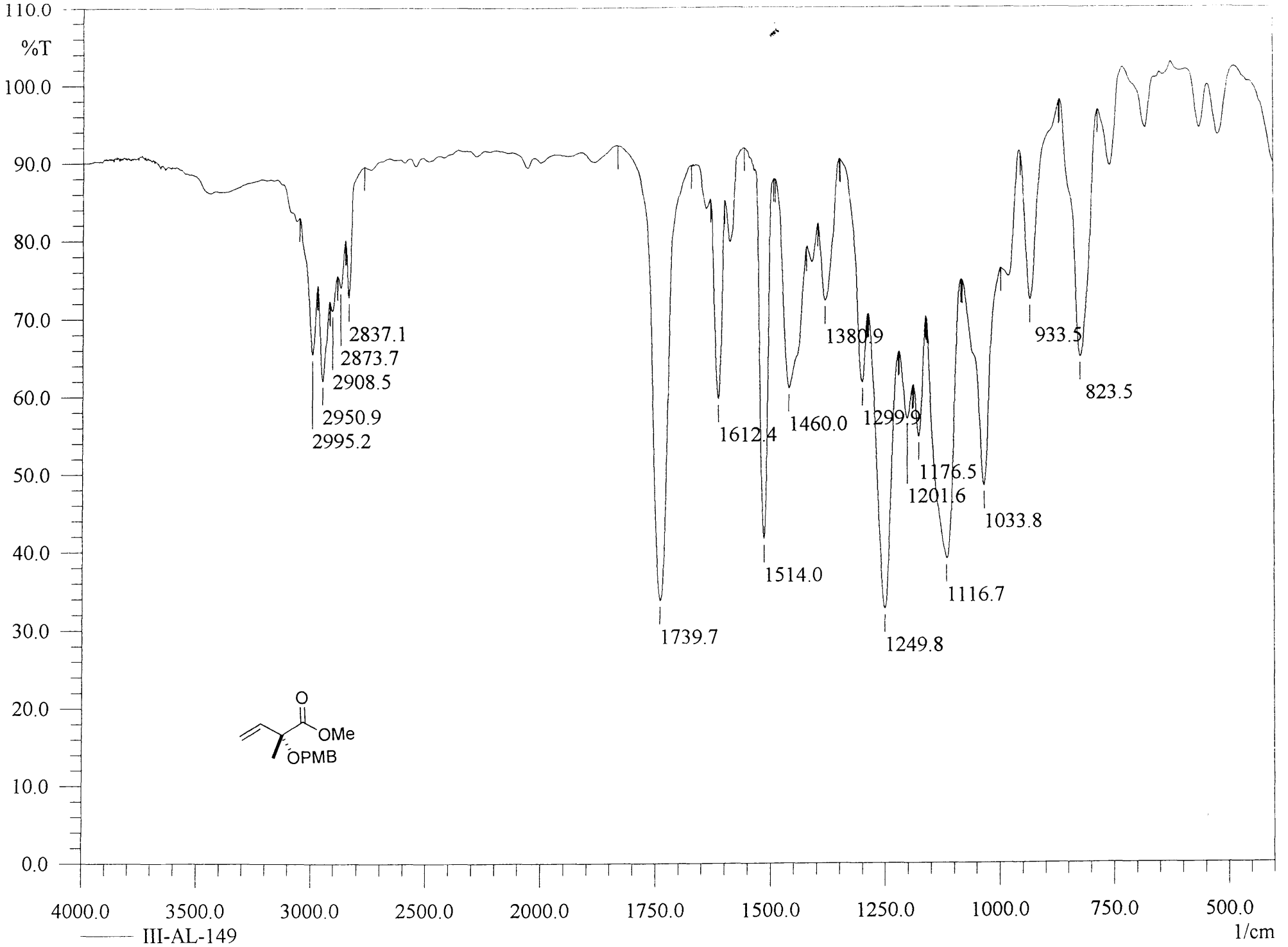


III-AL-149
HMBC
CDCl3 - 298K

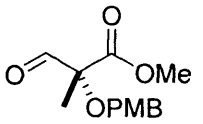




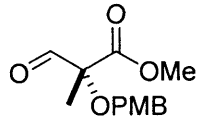

01191205: Scan Avg 132-133 (24.15 - 24.33 min) - Back
Base: 154.00 Int: 600839 Sample: VG 70-SE Positive Ion FAB
Sample: III-AL-149
Instrument Resolution: 7000
Theoretical Mass: (M+H) 251.12833
Measured Mass: (M+H) 251.12869
Error: 1.43 ppm
O
OMe
OPMB
105%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
154
166
189
227
250
273
289
307
341
357
389
140
200
250
300
350
400
m/z

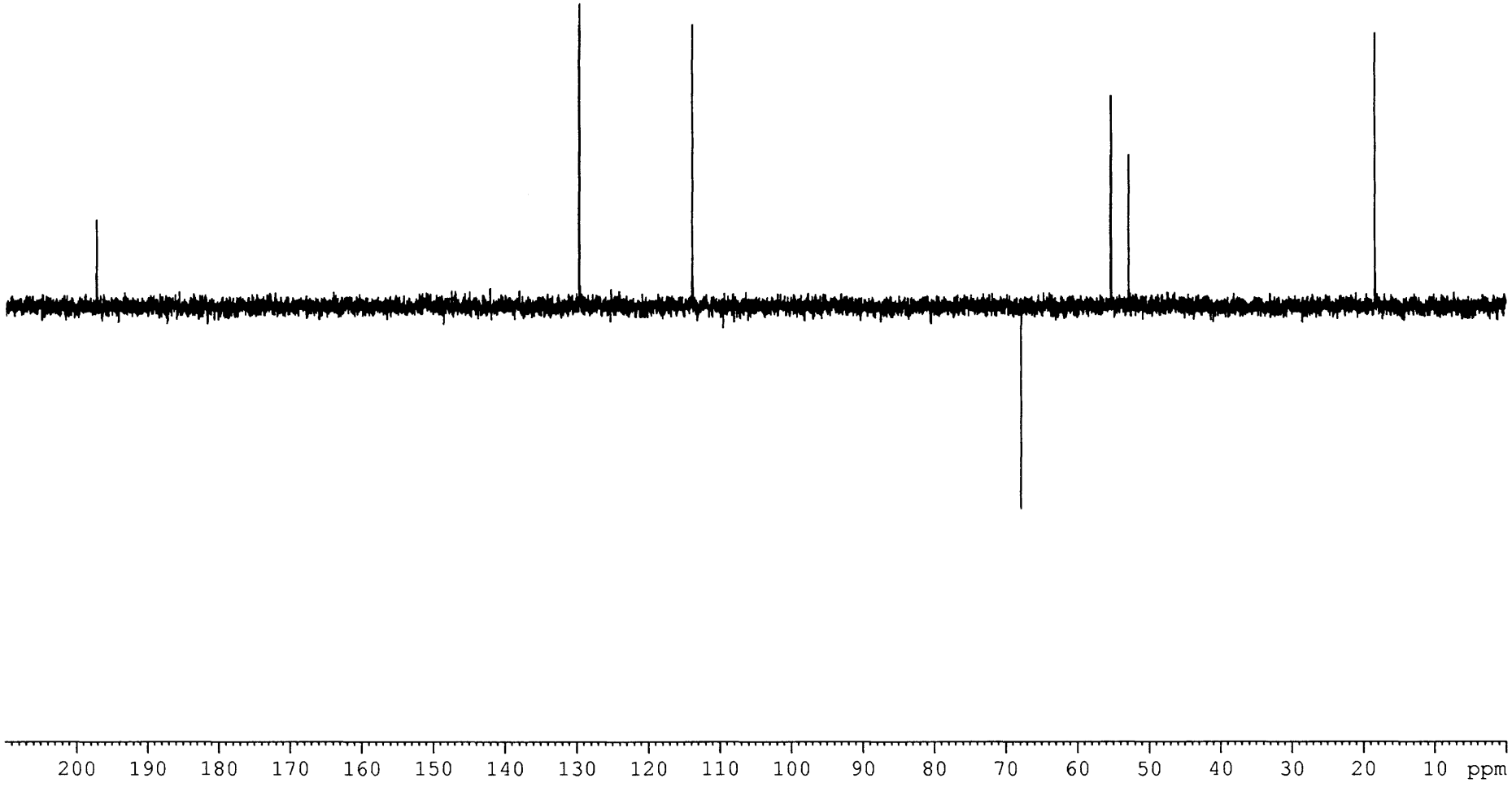

110.0
%T
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
2837.1
2873.7
2908.5
2950.9
2995.2
1612.4
1460.0
1380.9
1299.9
1176.5
1201.6
1033.8
933.5
823.5
1739.7
1514.0
1116.7
1249.8
O
OMe
OPMB
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
III-AL-149

IV-AL-105
CDCl3 - 298K

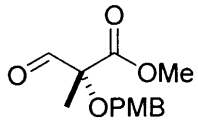


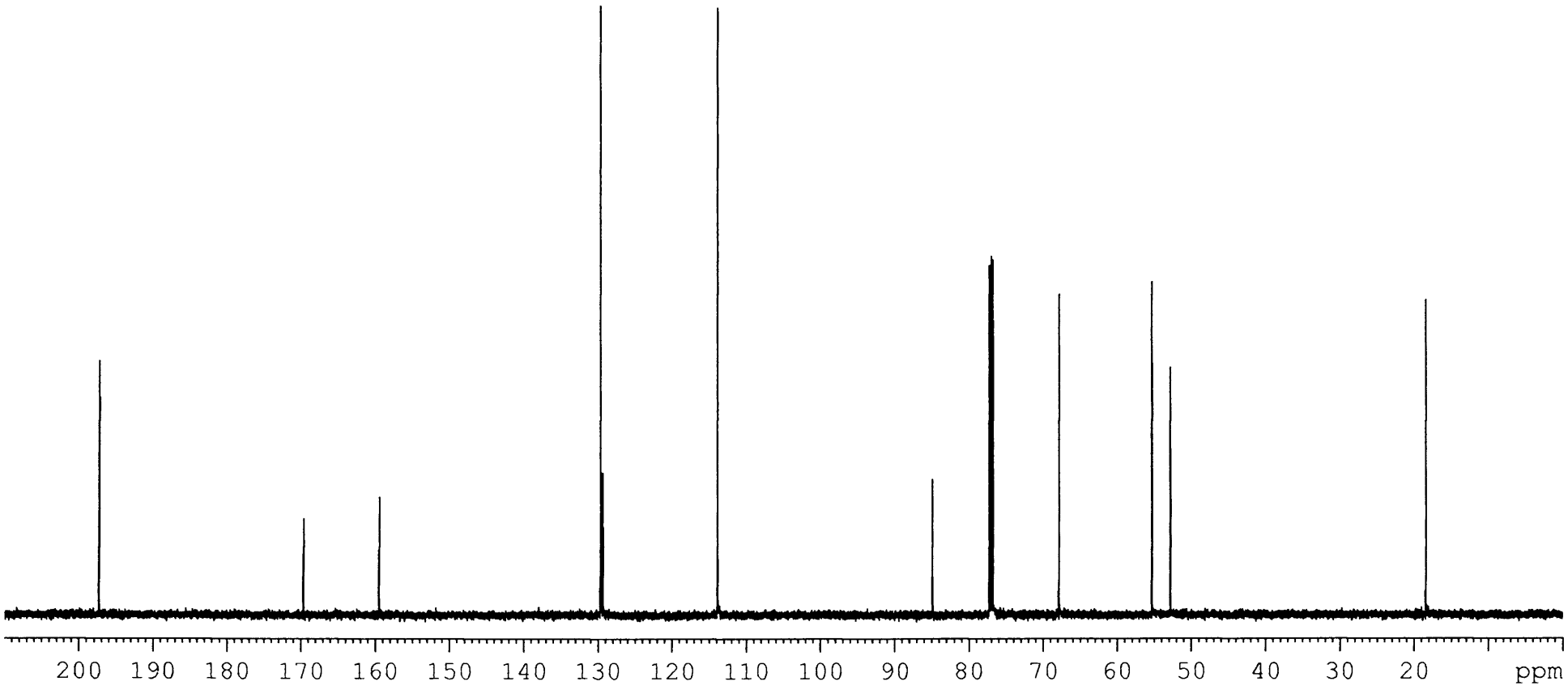
IV-AL-105
DEPT
CDCl3 - 298K



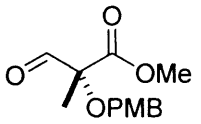


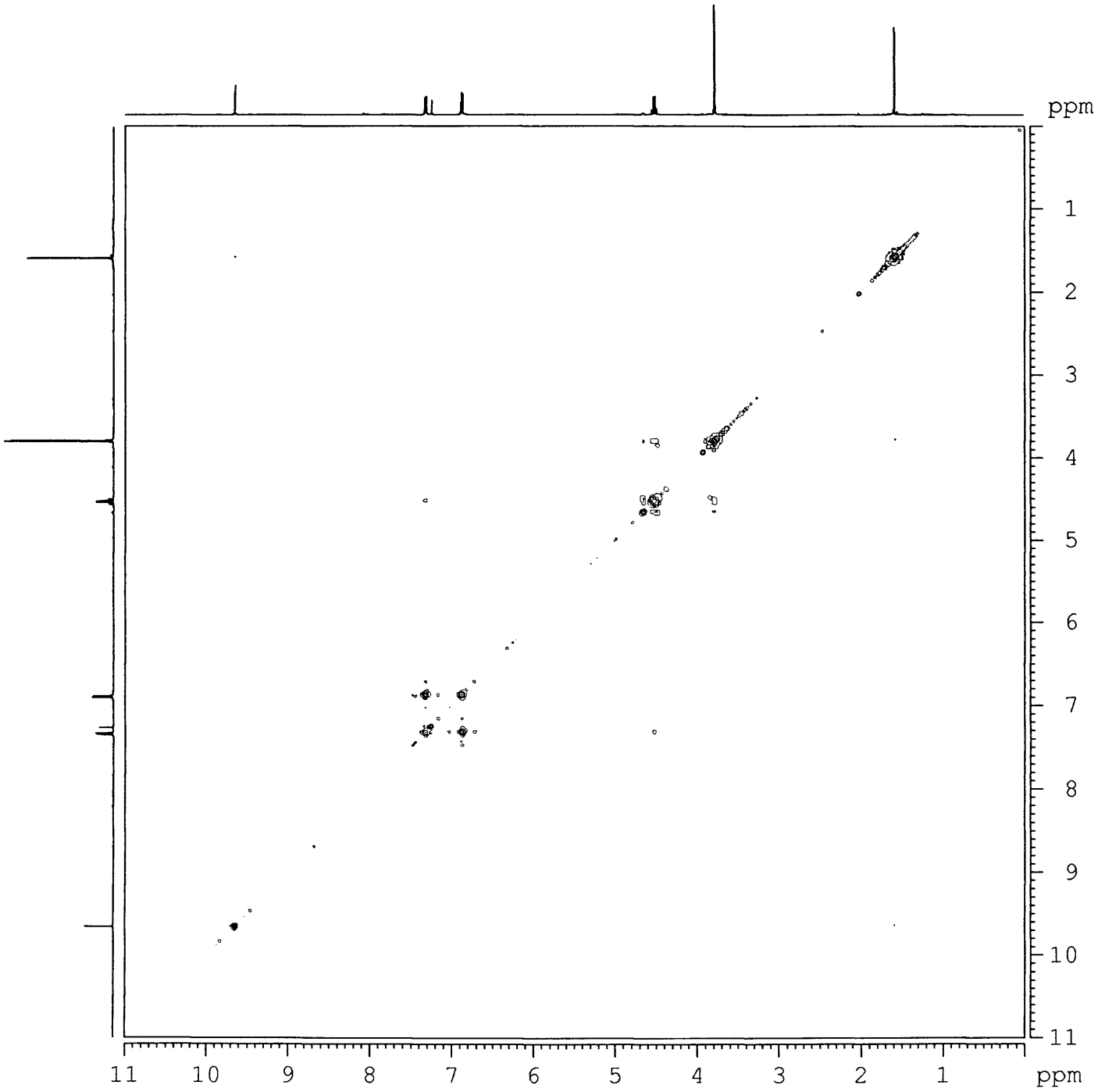
IV-AL-105
13C
295K- CDCl3

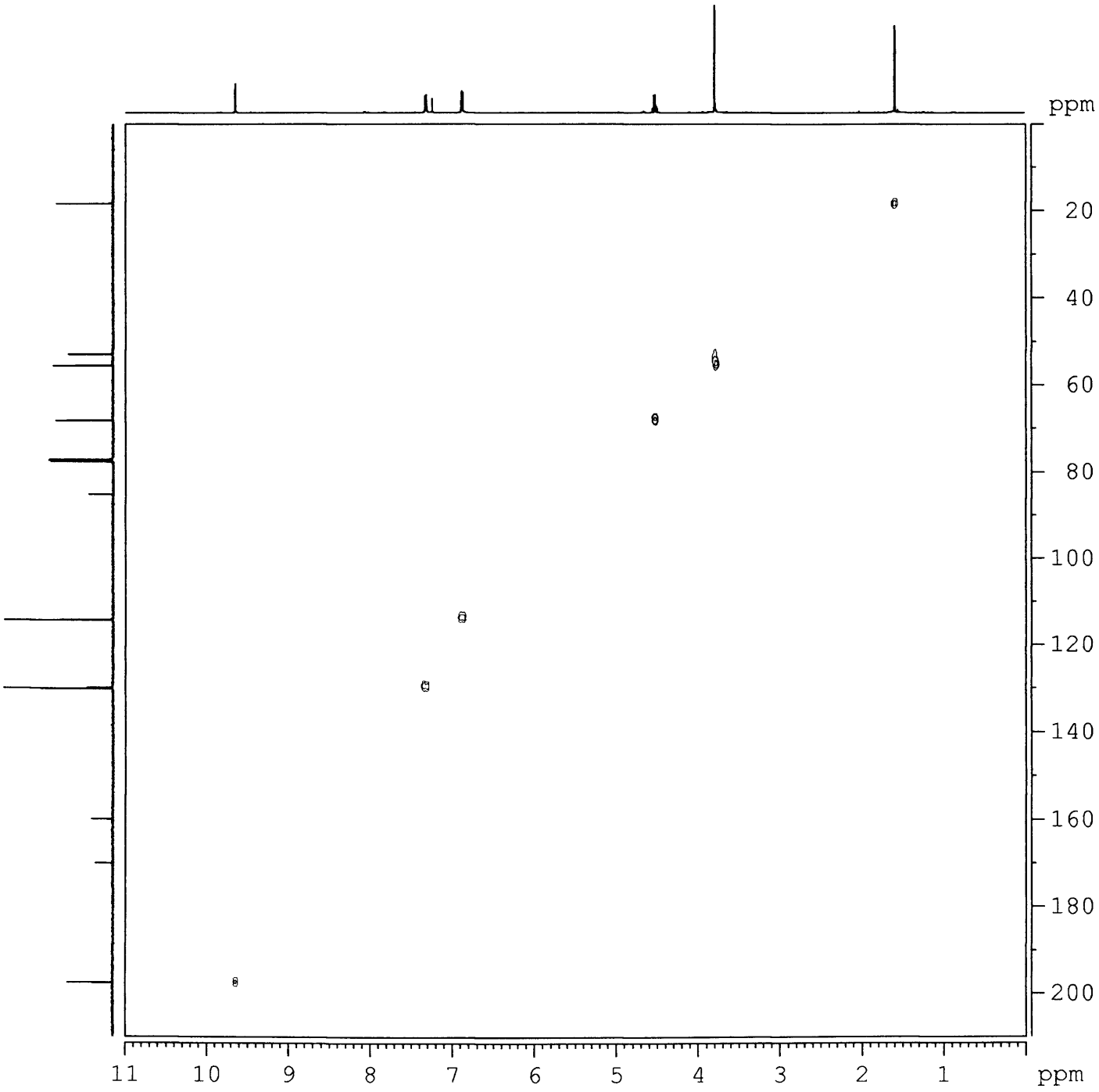




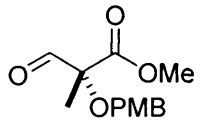
IV-AL-105
cosy
CDCl3 - 298K



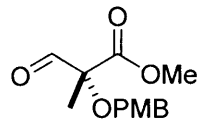


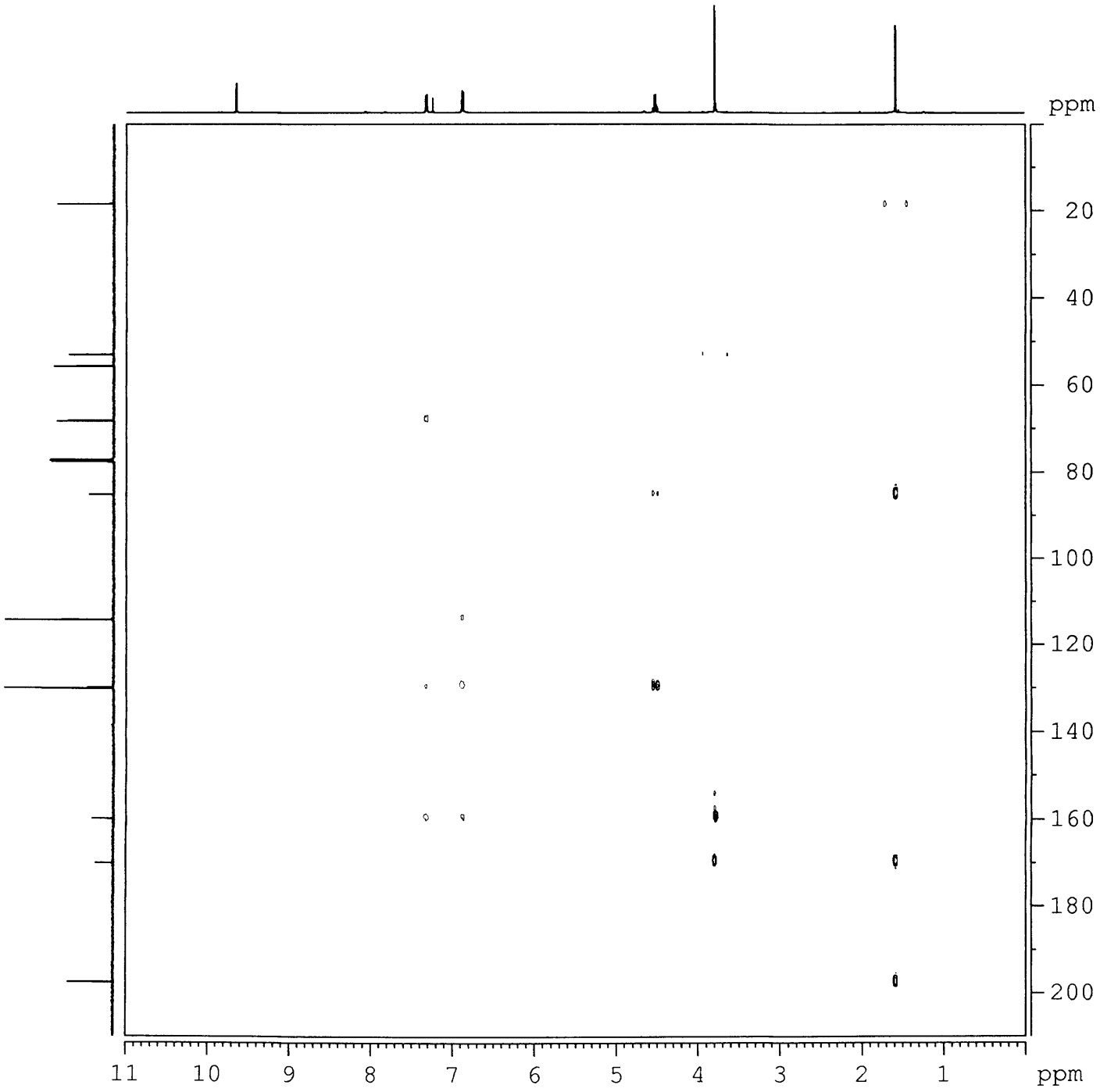


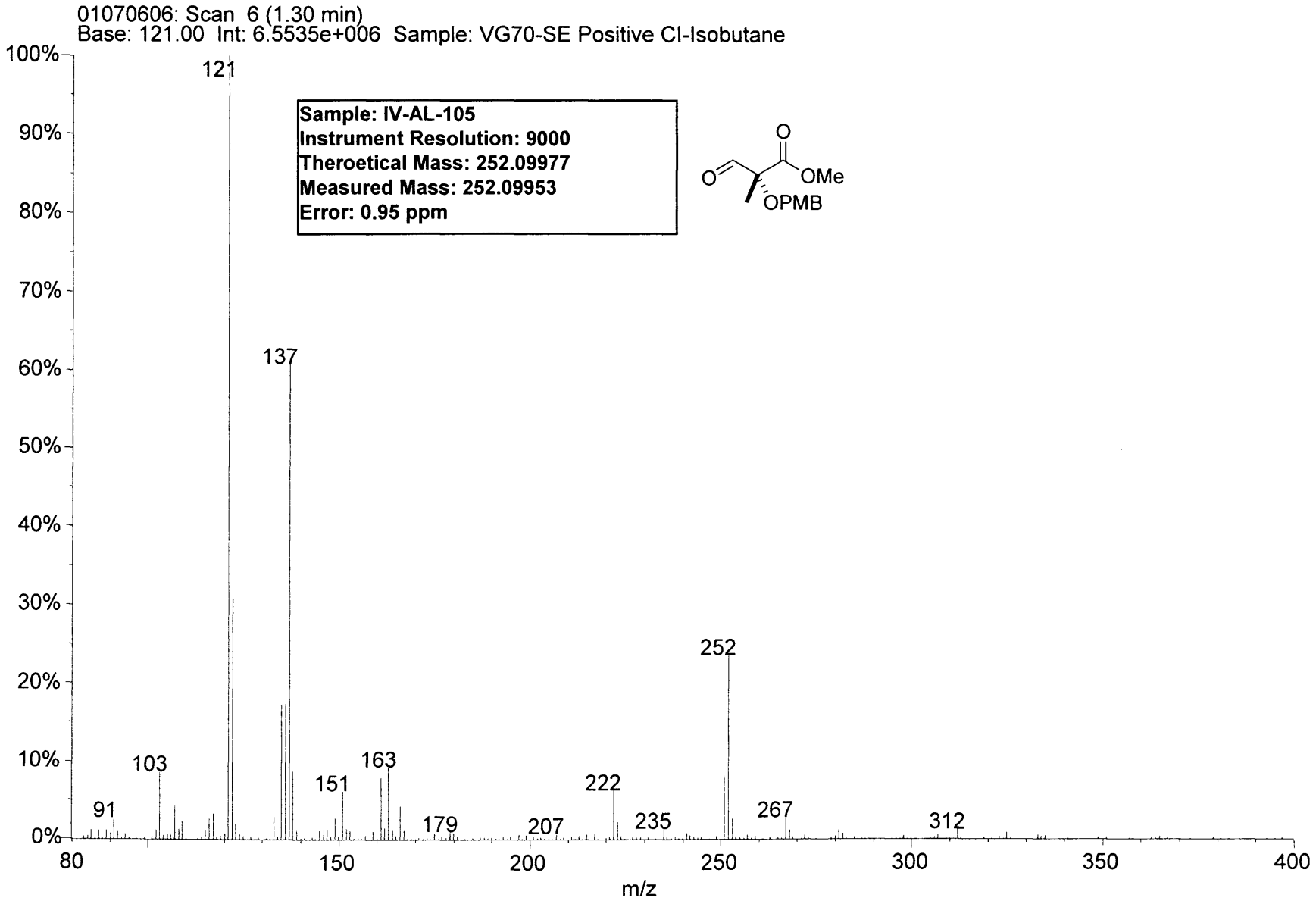
IV-AL-105
HMQC
295K- CDCl3

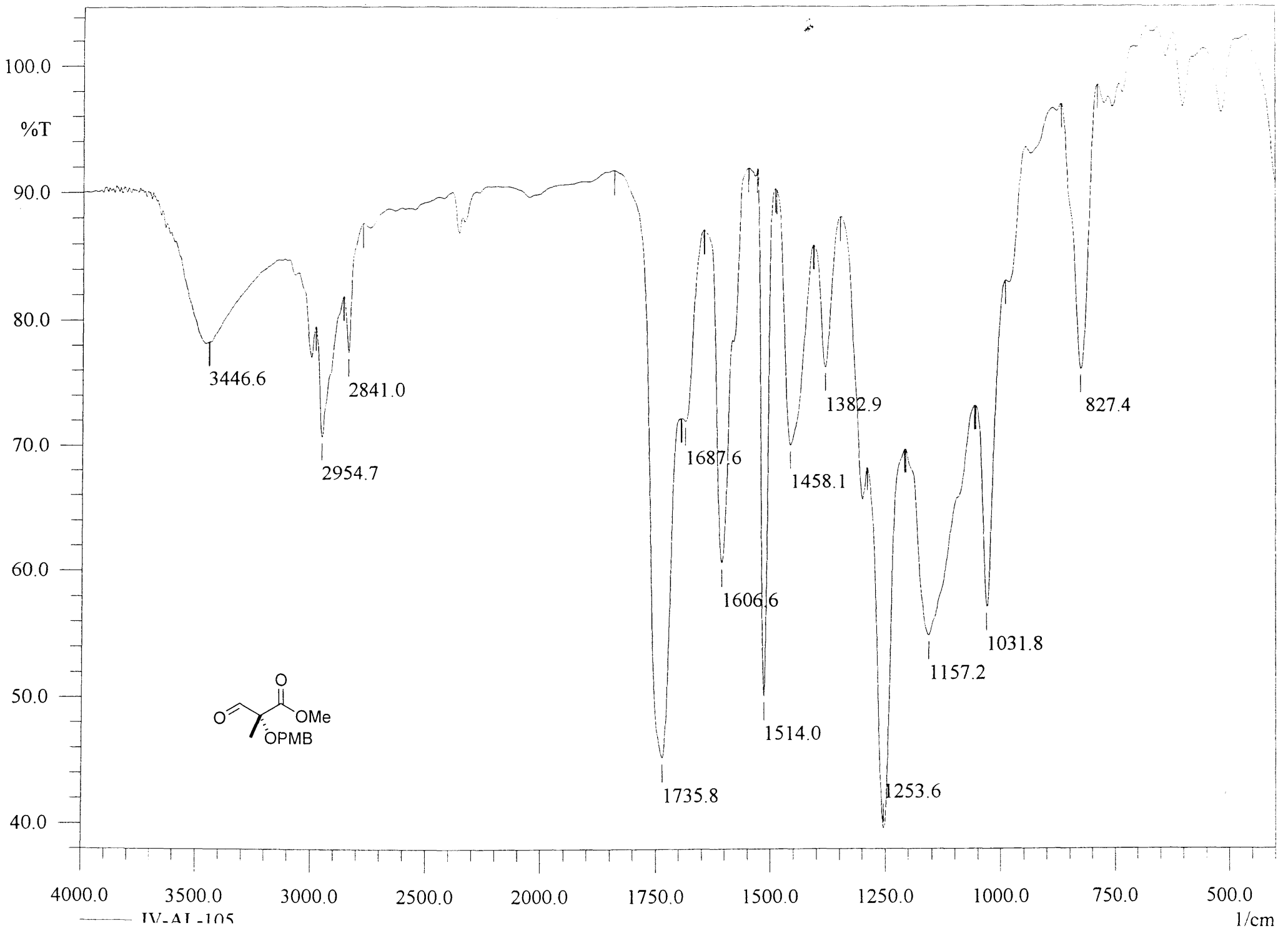


IV-AL-105
HMBC
295K- CDCl3

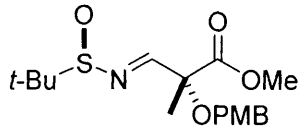




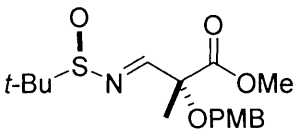

01070606: Scan 6 (1.30 min)
Base: 121.00 Int: 6.5535e+006 Sample: VG70-SE Positive CI-Isobutane
Sample: IV-AL-105
Instrument Resolution: 9000
Theroetical Mass: 252.09977
Measured Mass: 252.09953
Error: 0.95 ppm
O
OMe
OPMB
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
121
137
252
103
163
151
222
91
179
207
235
267
312
80
150
200
250
300
350
400
m/z

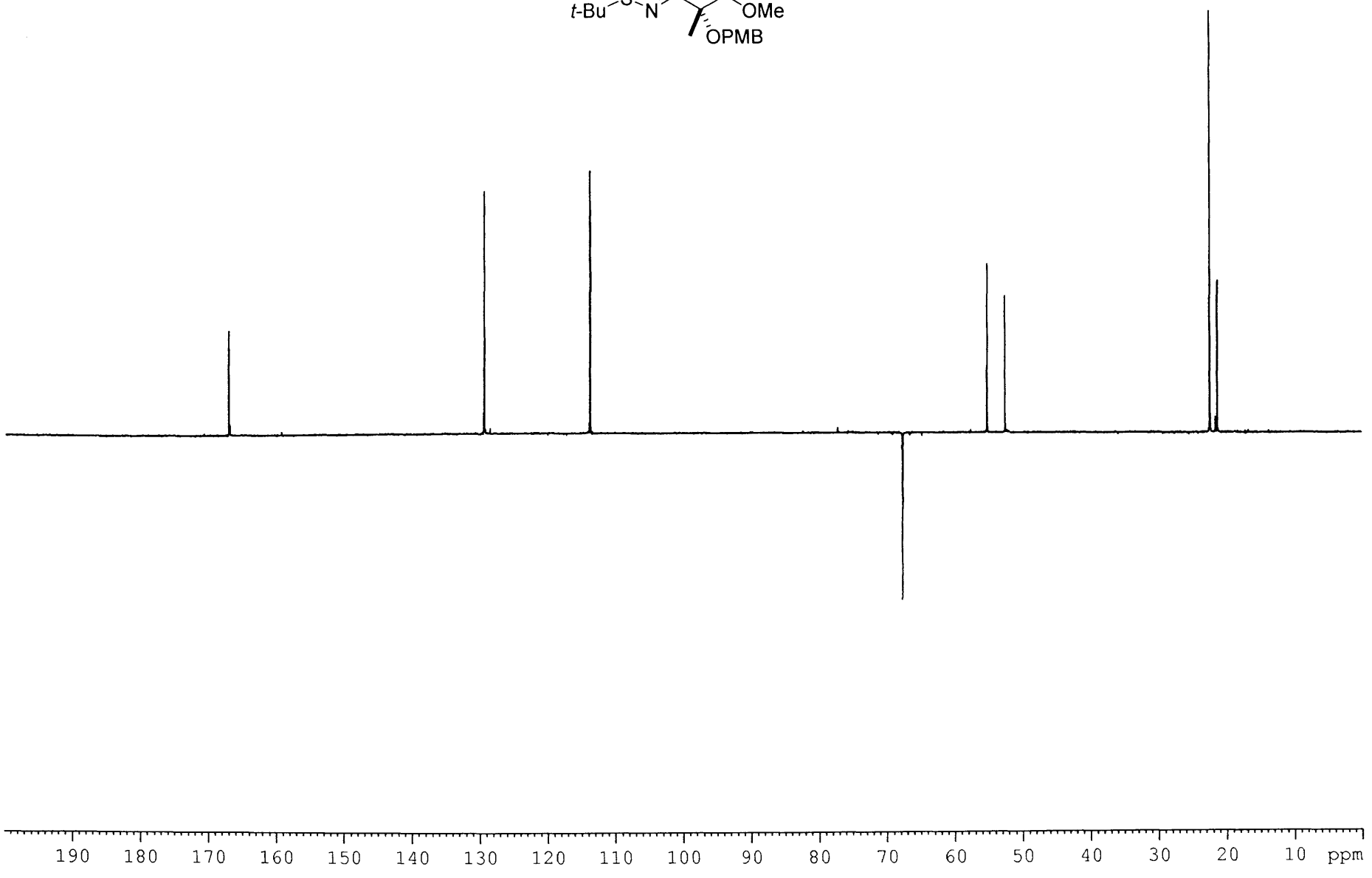

100.0
%T
90.0
80.0
70.0
60.0
50.0
40.0
3446.6
2954.7
2841.0
1687.6
1606.6
1514.0
1458.1
1382.9
1735.8
1253.6
1157.2
1031.8
827.4
O
O
OMe
O
OPMB
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm

III-AL-180-2
CDCl3 - 298K

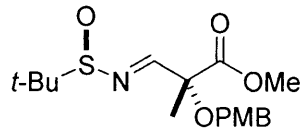


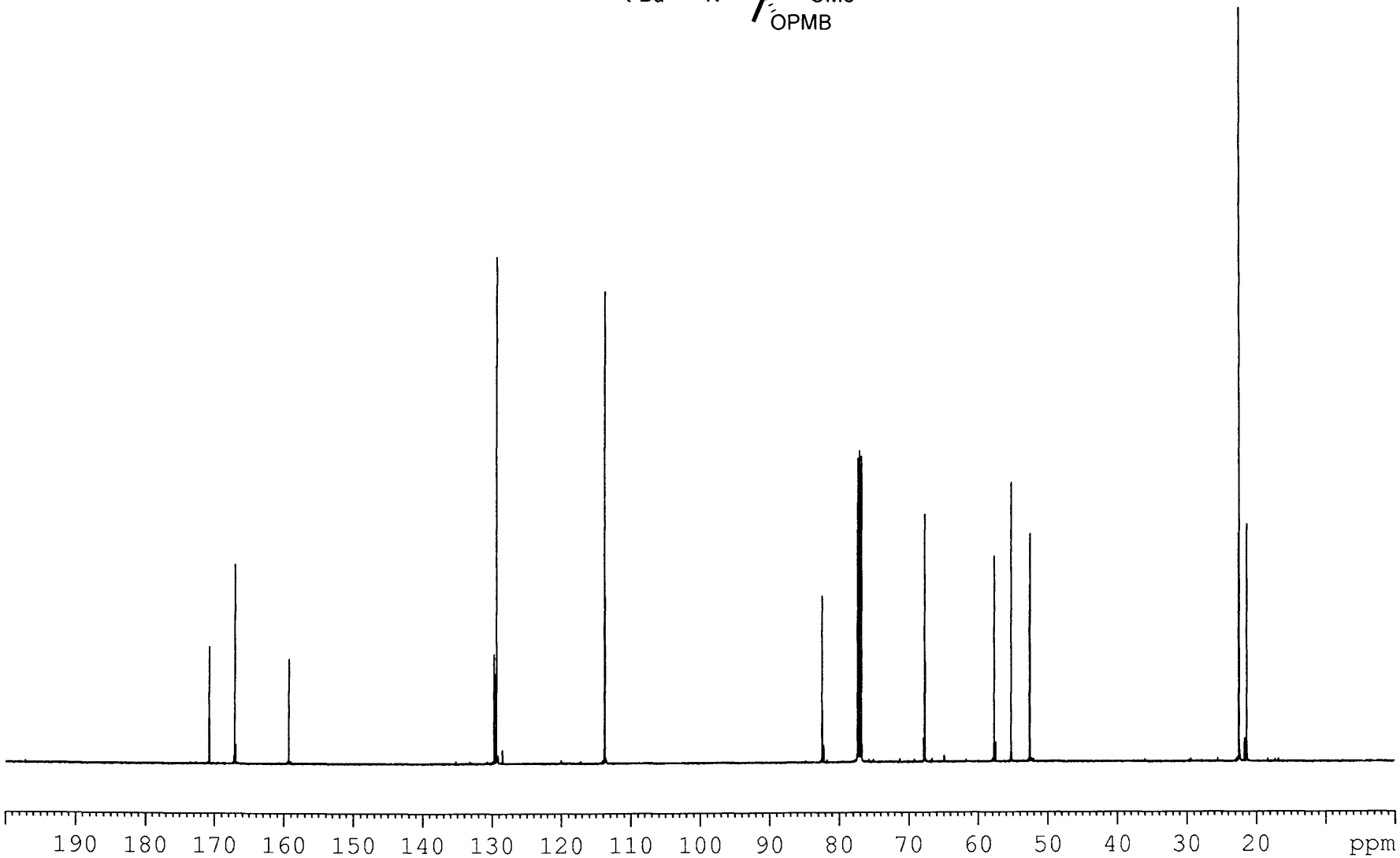
III-AL-180-2
dept
CDCl3 - 298K

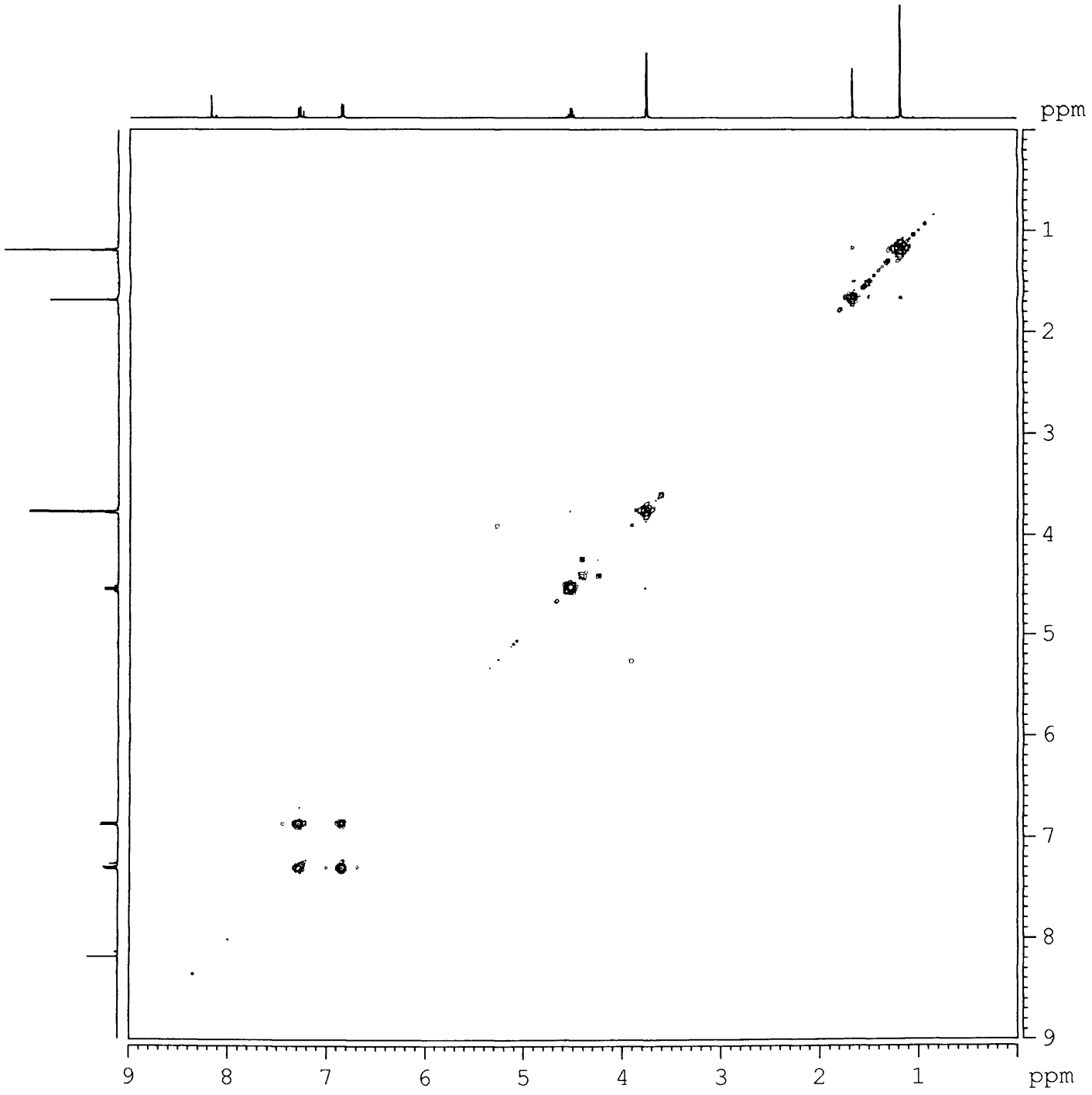




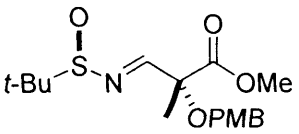
III-AL-180-2
13C
CDCl3 - 298K



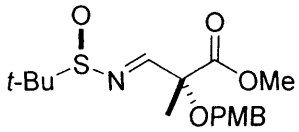


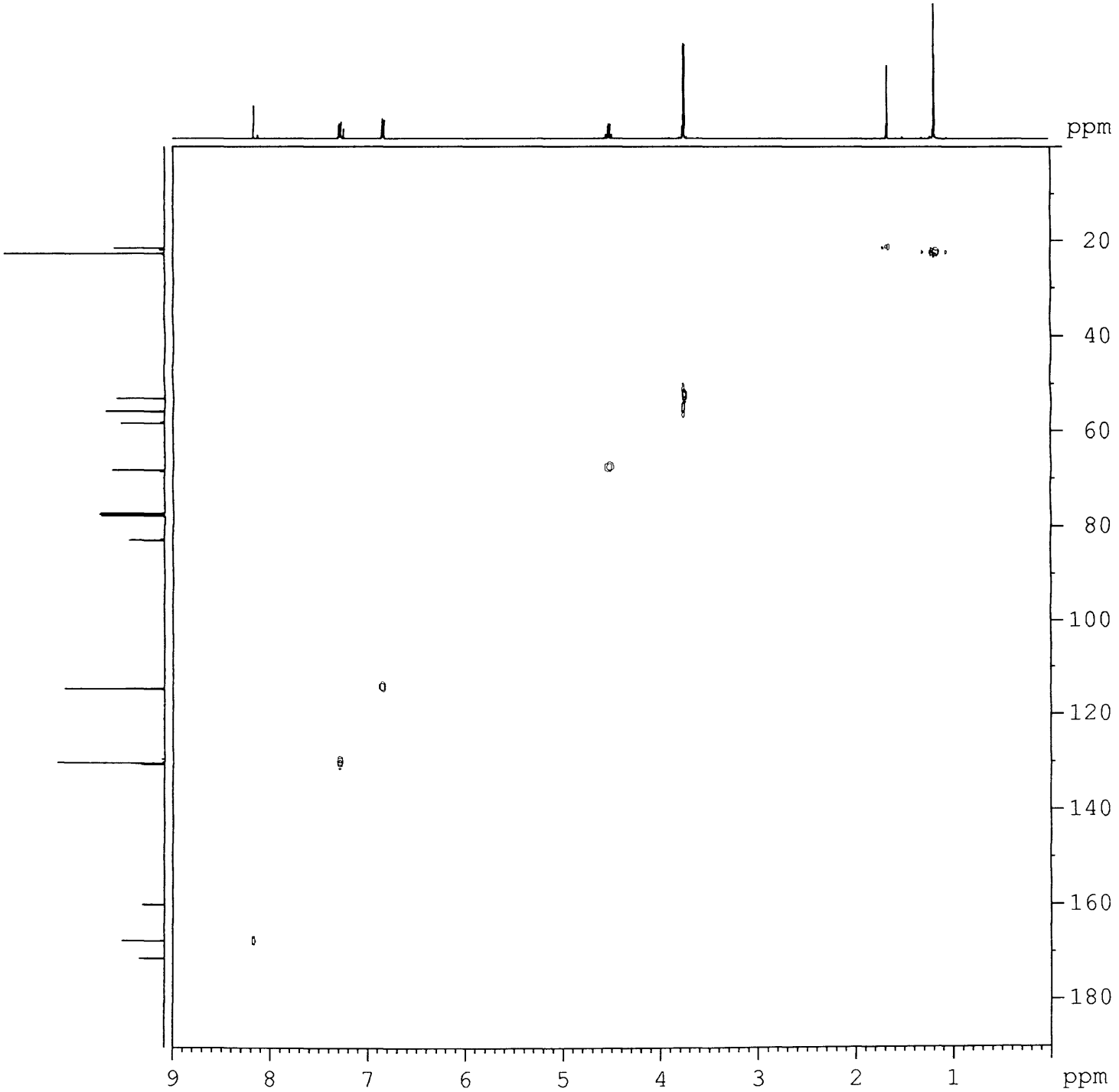


III-AL-180-2
COSY
CDCl3 - 298K

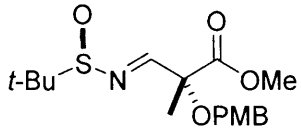


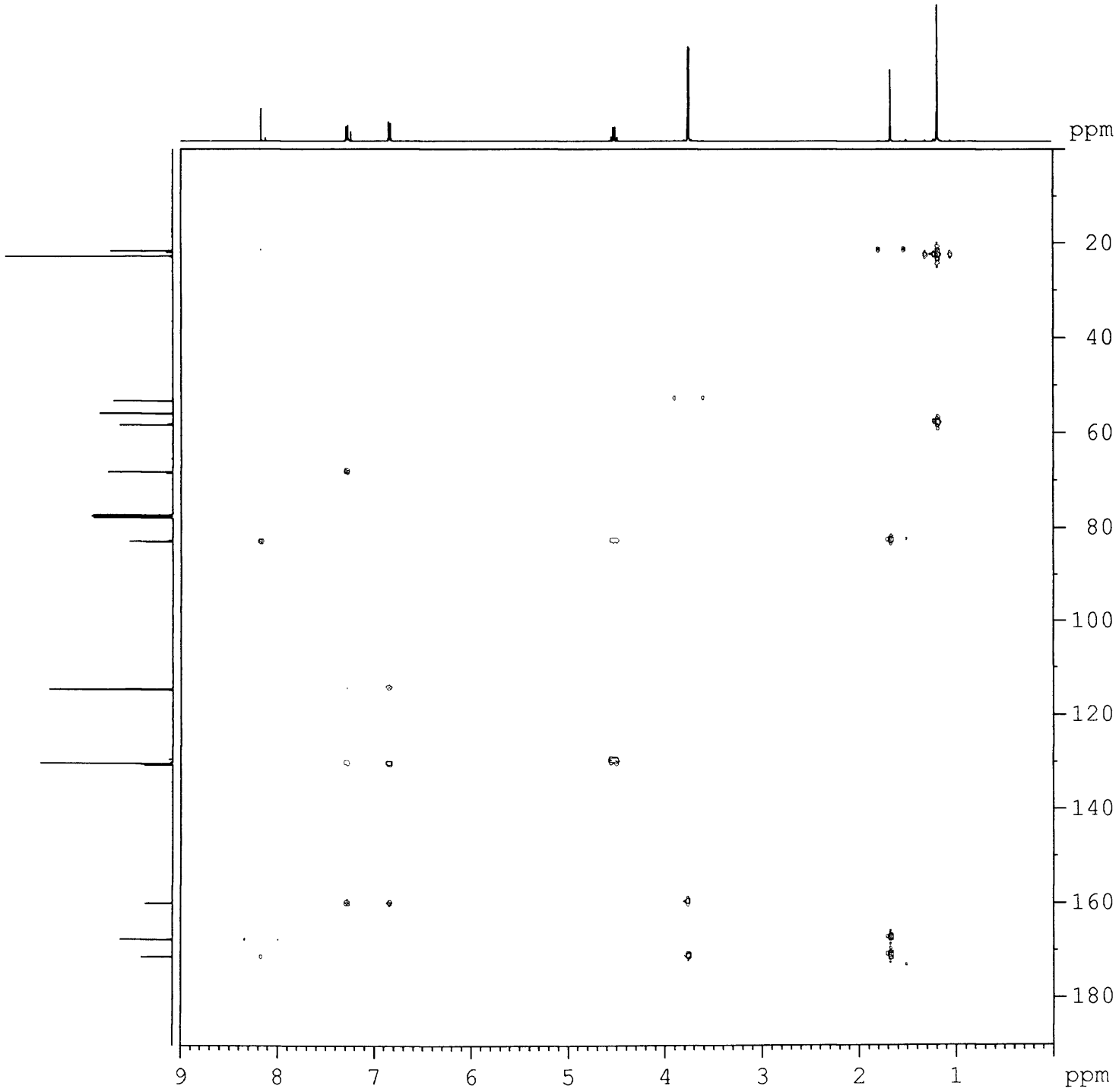
III-AL-180-2
HMQC
CDCl3 - 298K

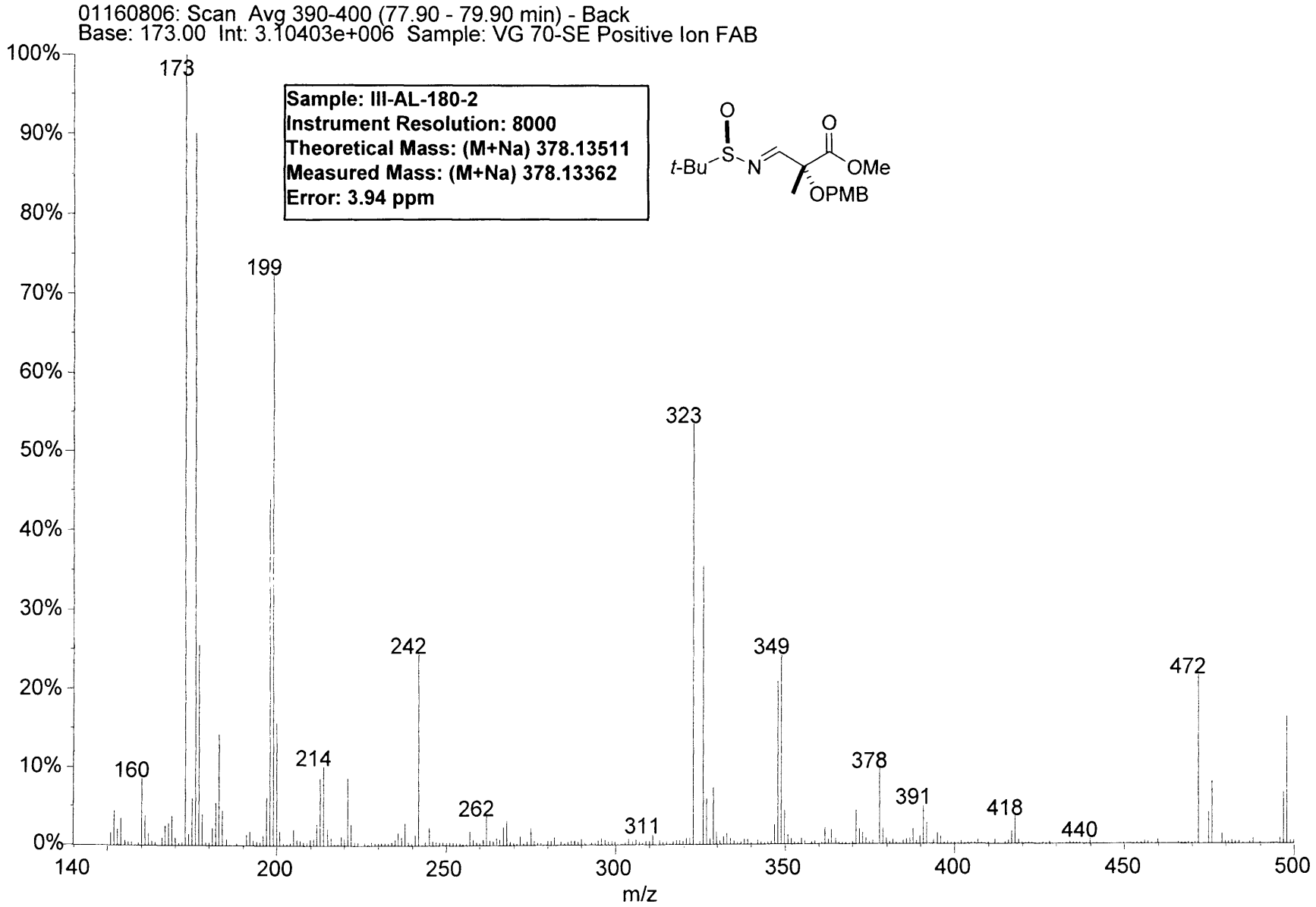


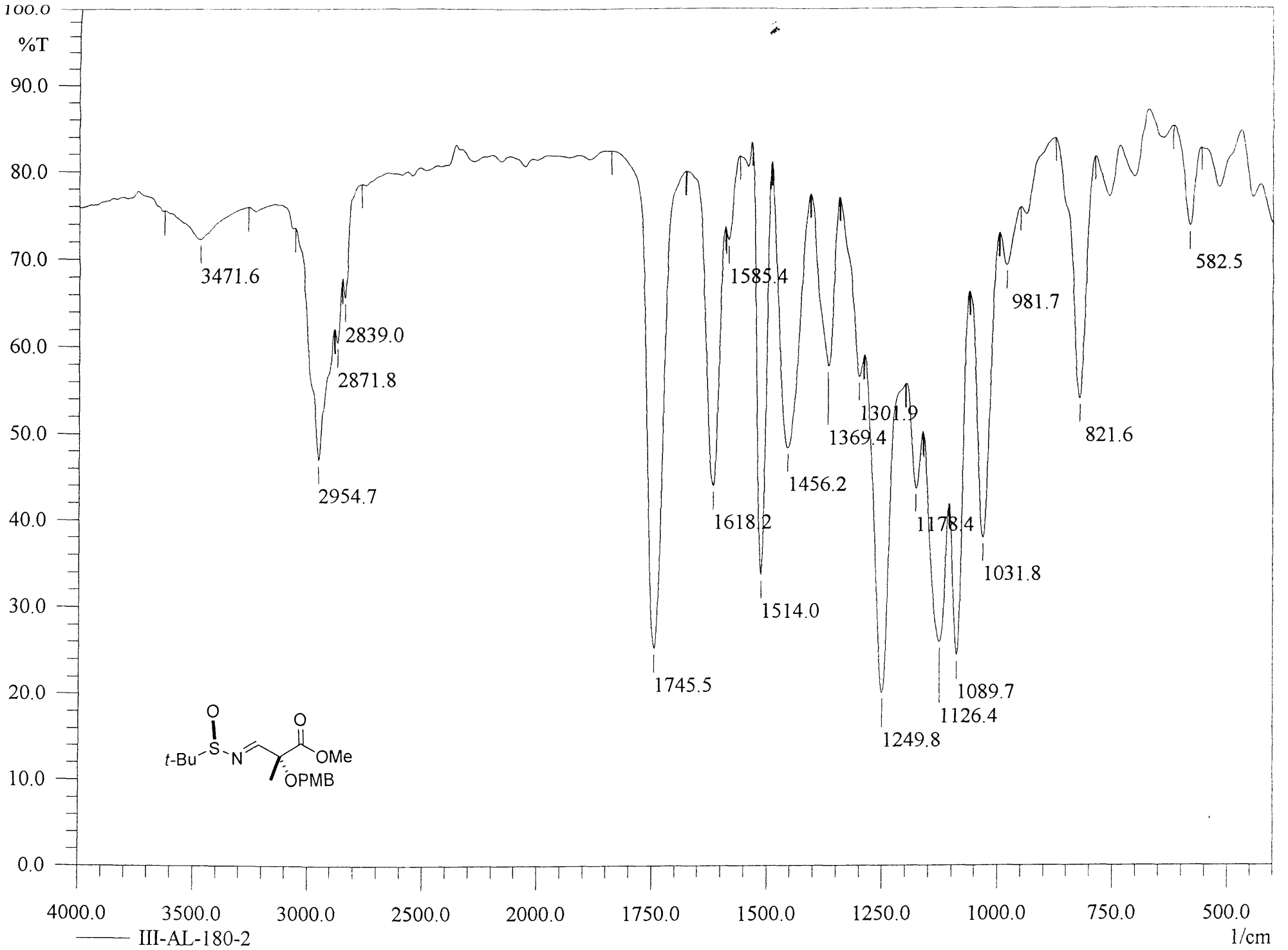


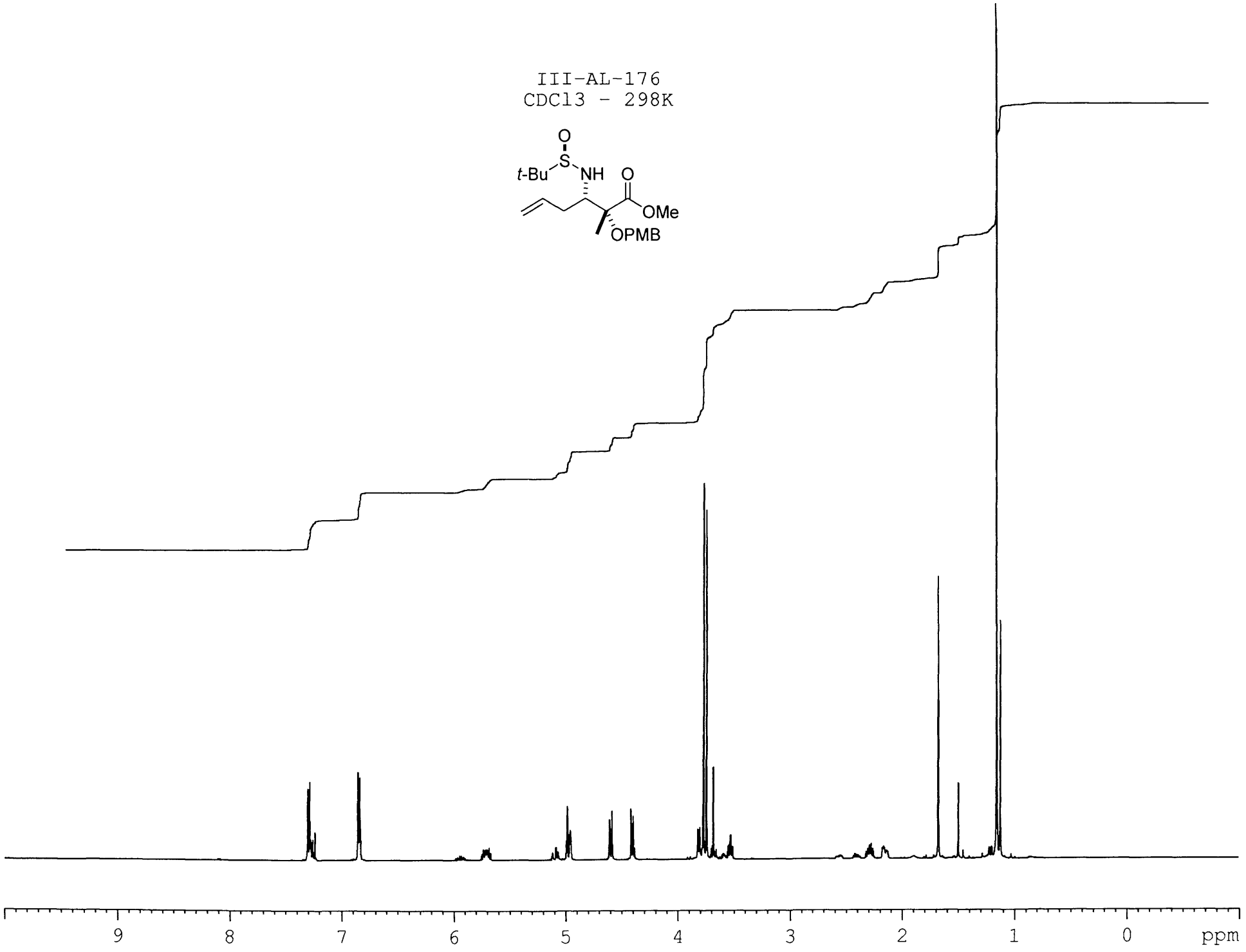
III-AL-180-2
HMBC
CDCl3 - 298K



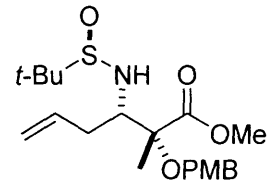



01160806: Scan Avg 390-400 (77.90 - 79.90 min) - Back
Base: 173.00 Int: 3.10403e+006 Sample: VG 70-SE Positive Ion FAB
Sample: III-AL-180-2
Instrument Resolution: 8000
Theoretical Mass: (M+Na) 378.13511
Measured Mass: (M+Na) 378.13362
Error: 3.94 ppm
t-Bu
S
N
O
O
OMe
OPMB
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
173
199
323
242
349
472
160
214
262
311
378
391
418
440
140
200
250
300
350
400
450
500
m/z

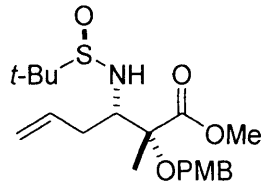

100.0
%T
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
3471.6
2954.7
2839.0
2871.8
1745.5
1618.2
1585.4
1514.0
1456.2
1369.4
1301.9
1249.8
1178.4
1126.4
1089.7
1031.8
981.7
821.6
582.5
t-Bu
S
N
O
O
OMe
OPMB
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
III-AL-180-2

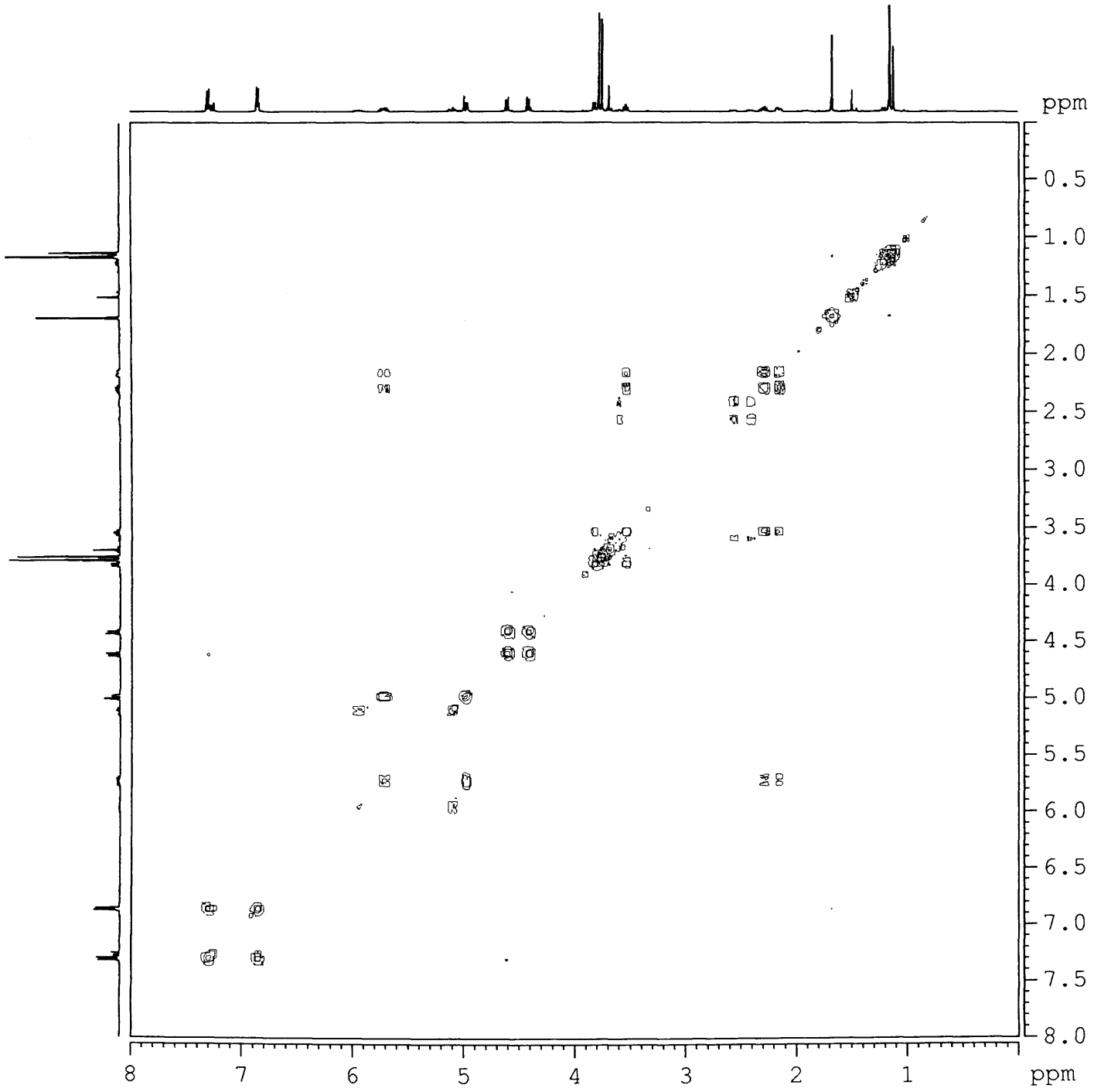

III-AL-176
CDCl3 - 298K
O
S
t-Bu
NH
O
OMe
OPMB
9
8
7
6
5
4
3
2
1
0
ppm

III-AL-176
DEPT
CDCl3 - 298K

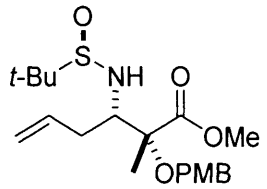


III-AL-176
13C
CDCl3 - 298K

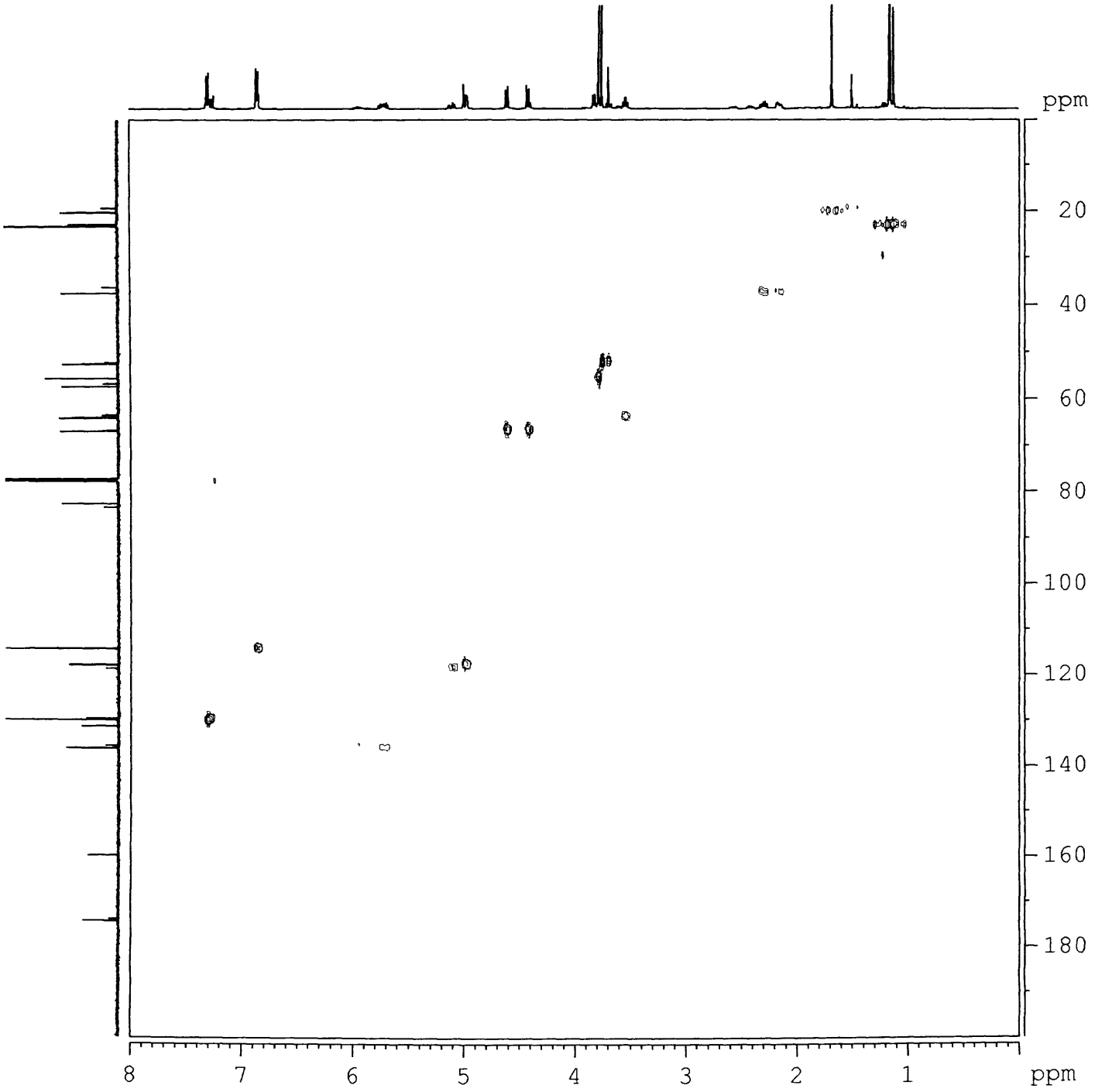


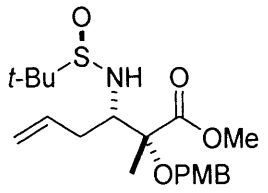


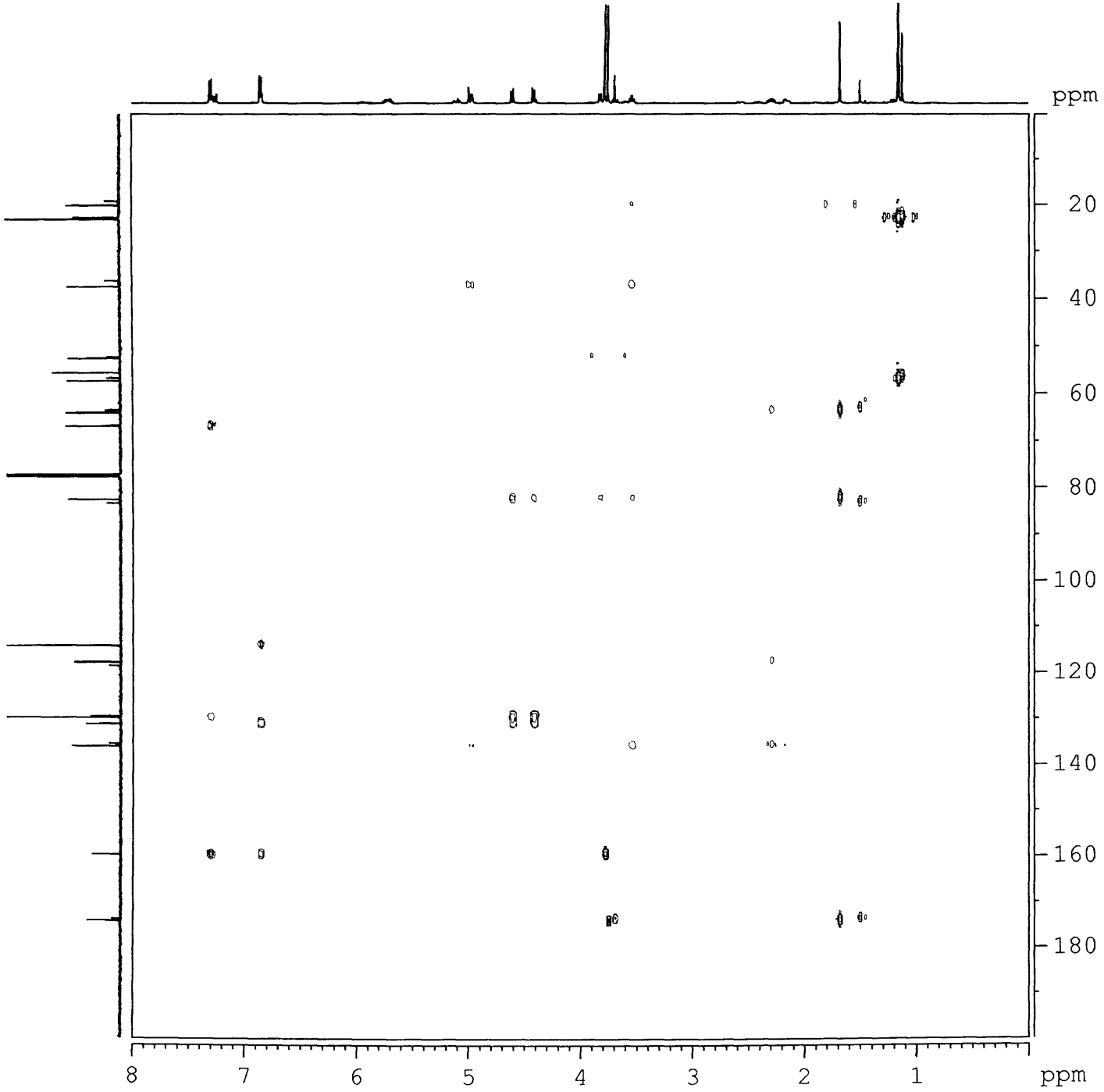
III-AL-176
COSY
CDCl3 - 298K



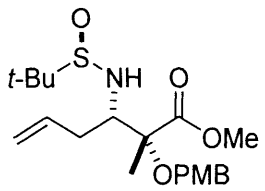
III-AL-176
HMQC
CDCl3 - 298K

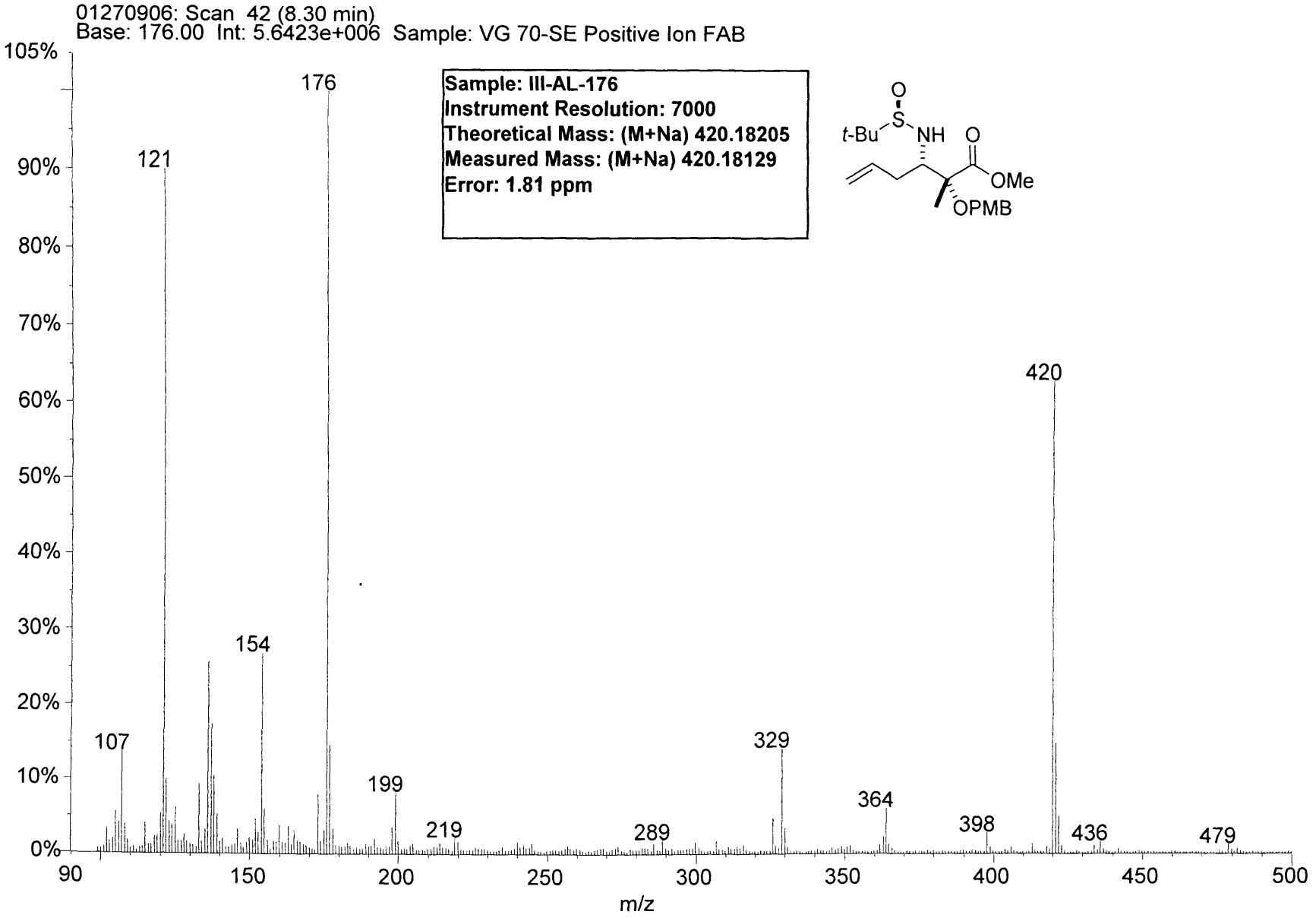


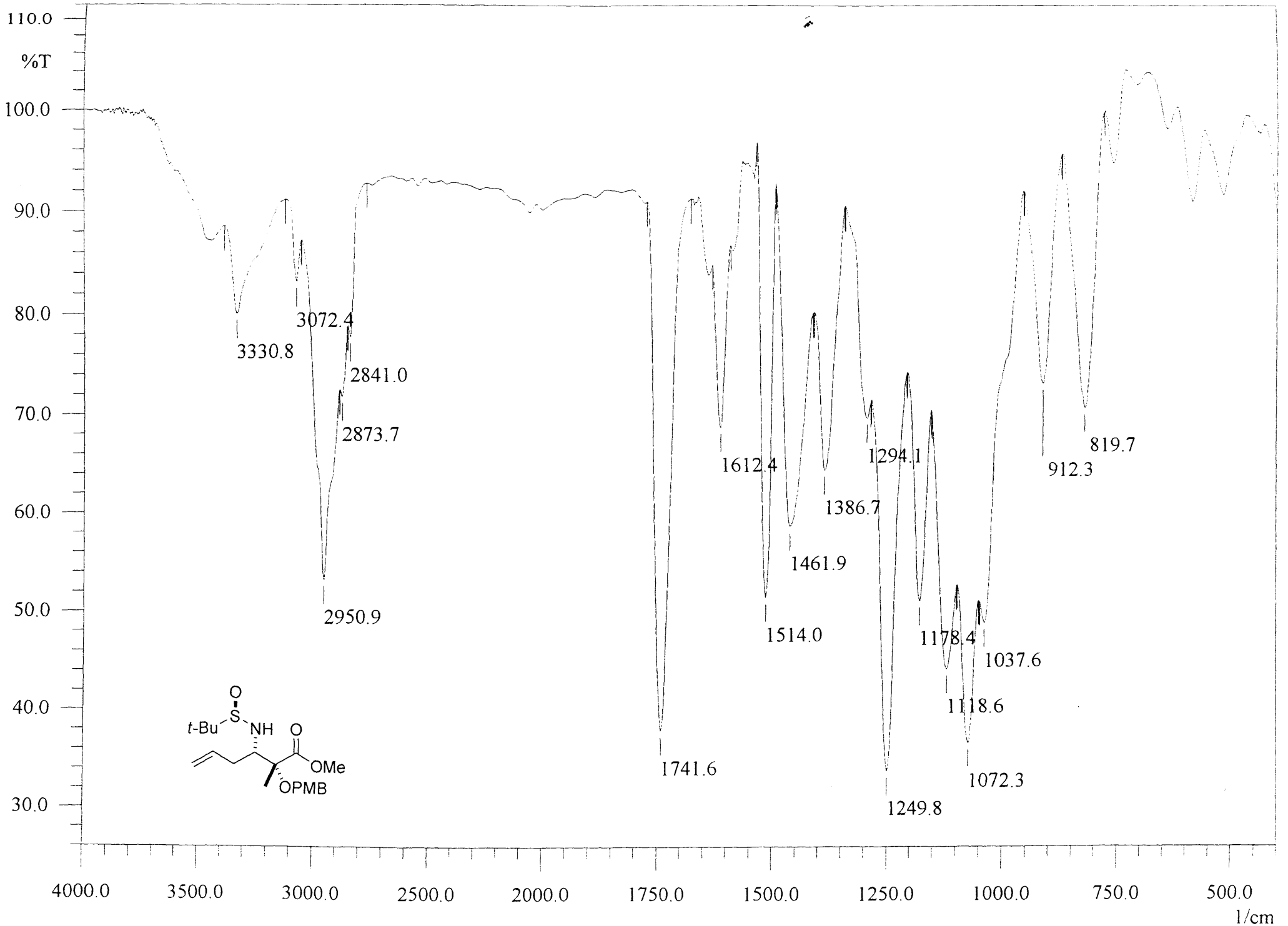


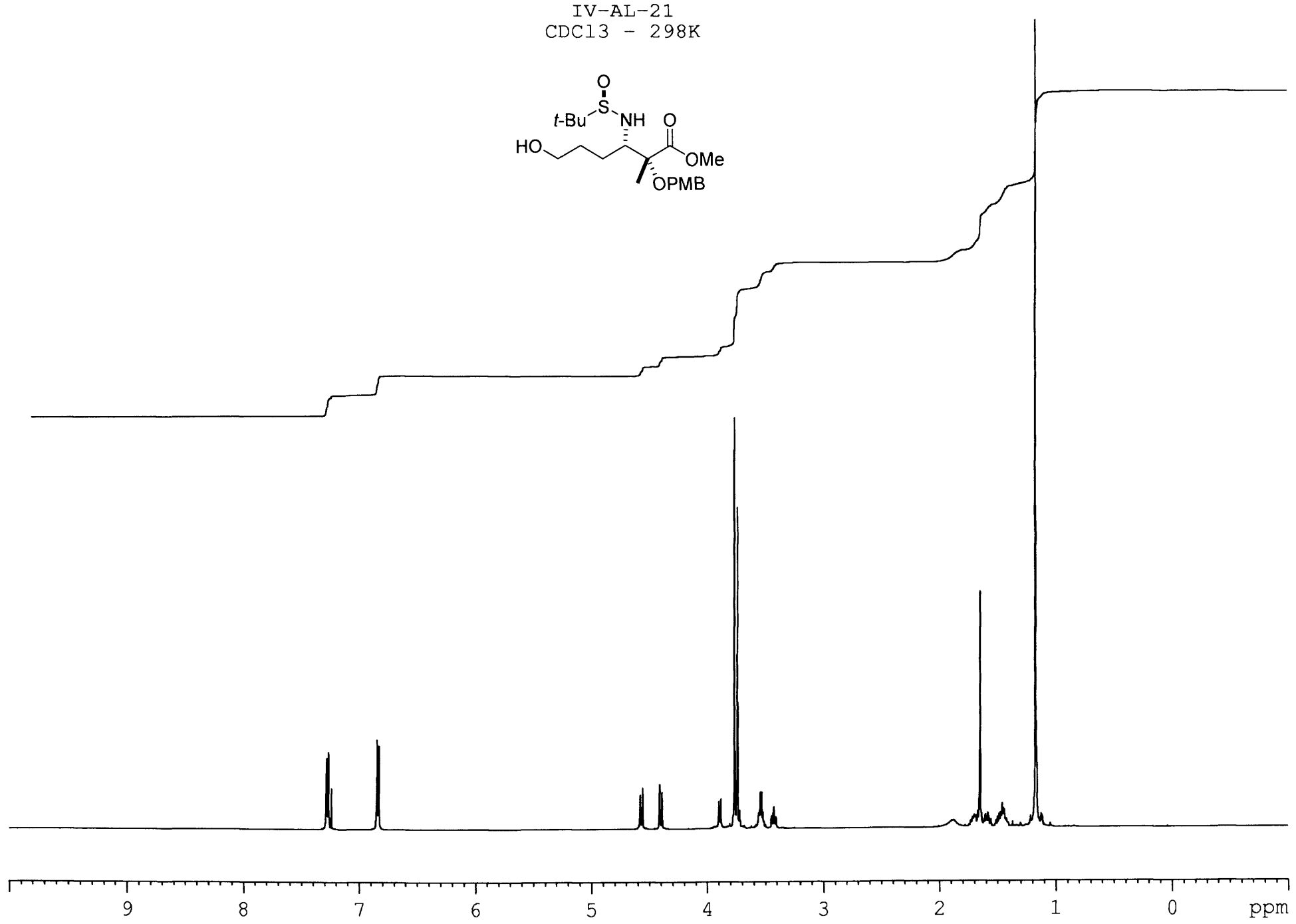


III-AL-176
HMBC
CDCl3 - 298K

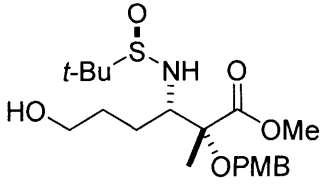



01270906: Scan 42 (8.30 min)
Base: 176.00 Int: 5.6423e+006 Sample: VG 70-SE Positive Ion FAB
Sample: III-AL-176
Instrument Resolution: 7000
Theoretical Mass: (M+Na) 420.18205
Measured Mass: (M+Na) 420.18129
Error: 1.81 ppm
t-Bu
NH
OMe
OPMB
105%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
176
121
420
154
107
329
199
364
219
289
398
436
479
90
150
200
250
300
350
400
450
500
m/z

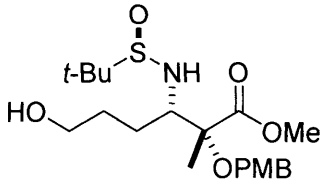

110.0
%T
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
3330.8
3072.4
2841.0
2873.7
2950.9
1741.6
1612.4
1514.0
1461.9
1386.7
1294.1
1249.8
1178.4
1118.6
1072.3
1037.6
912.3
819.7
O
S
t-Bu
NH
O
OMe
OPMB
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm

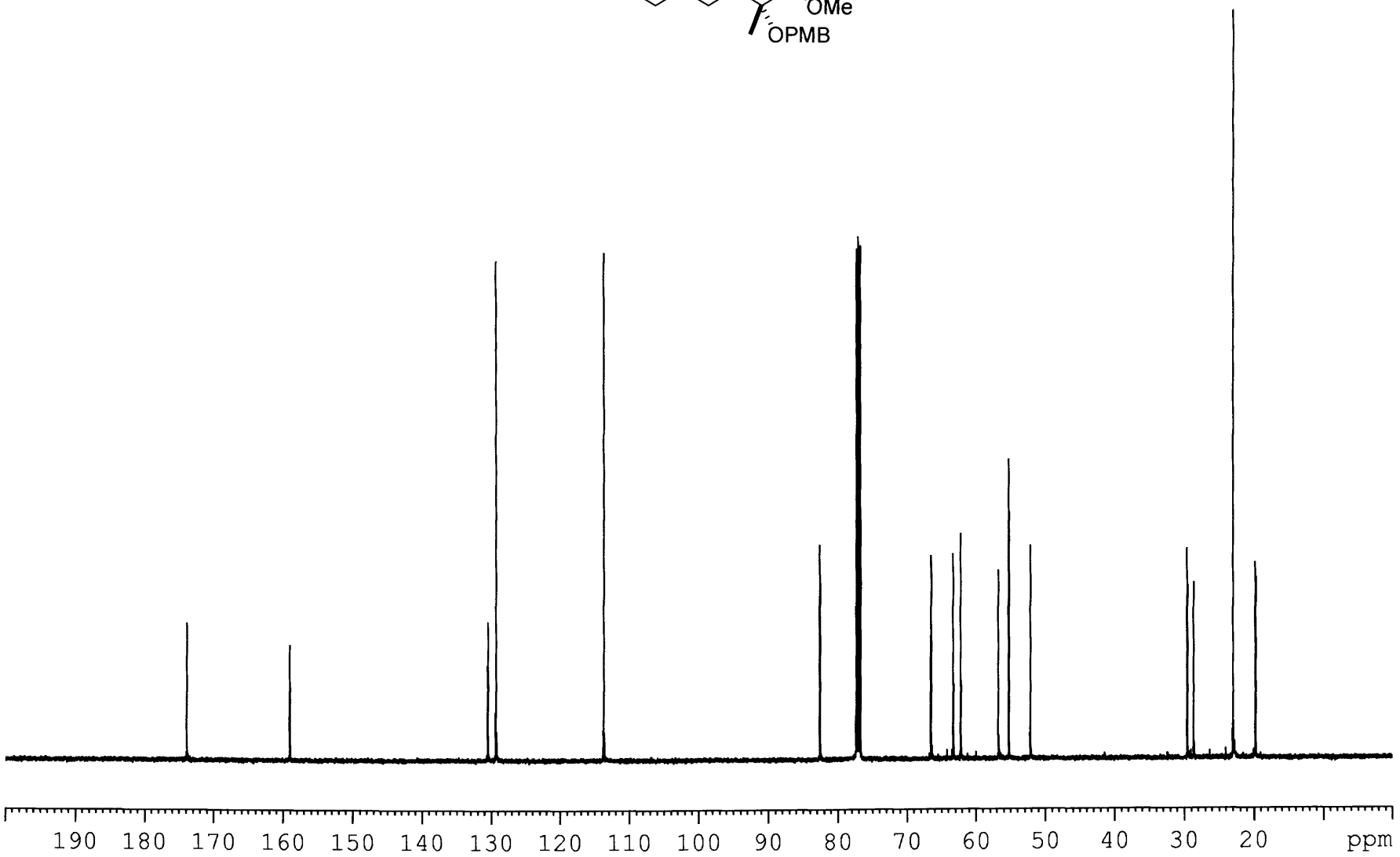

IV-AL-21
CDCl3 - 298K
O
S
t-Bu
NH
O
HO
OMe
OPMB
9
8
7
6
5
4
3
2
1
0
ppm

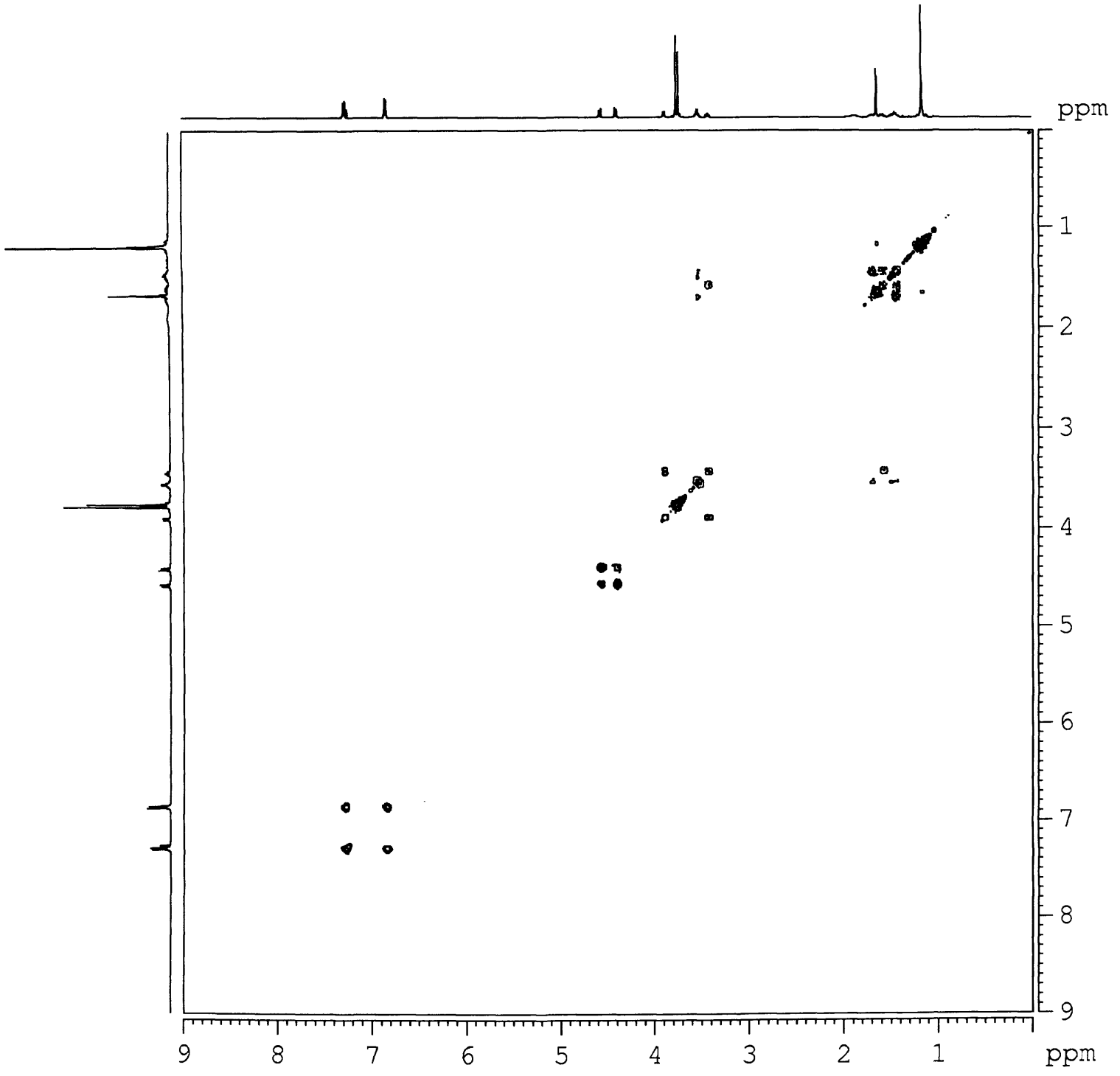
IV-AL-21
DEPT
CDCl3 - 298K



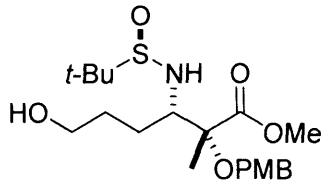
IV-AL-21
13C
CDCl3 - 298K

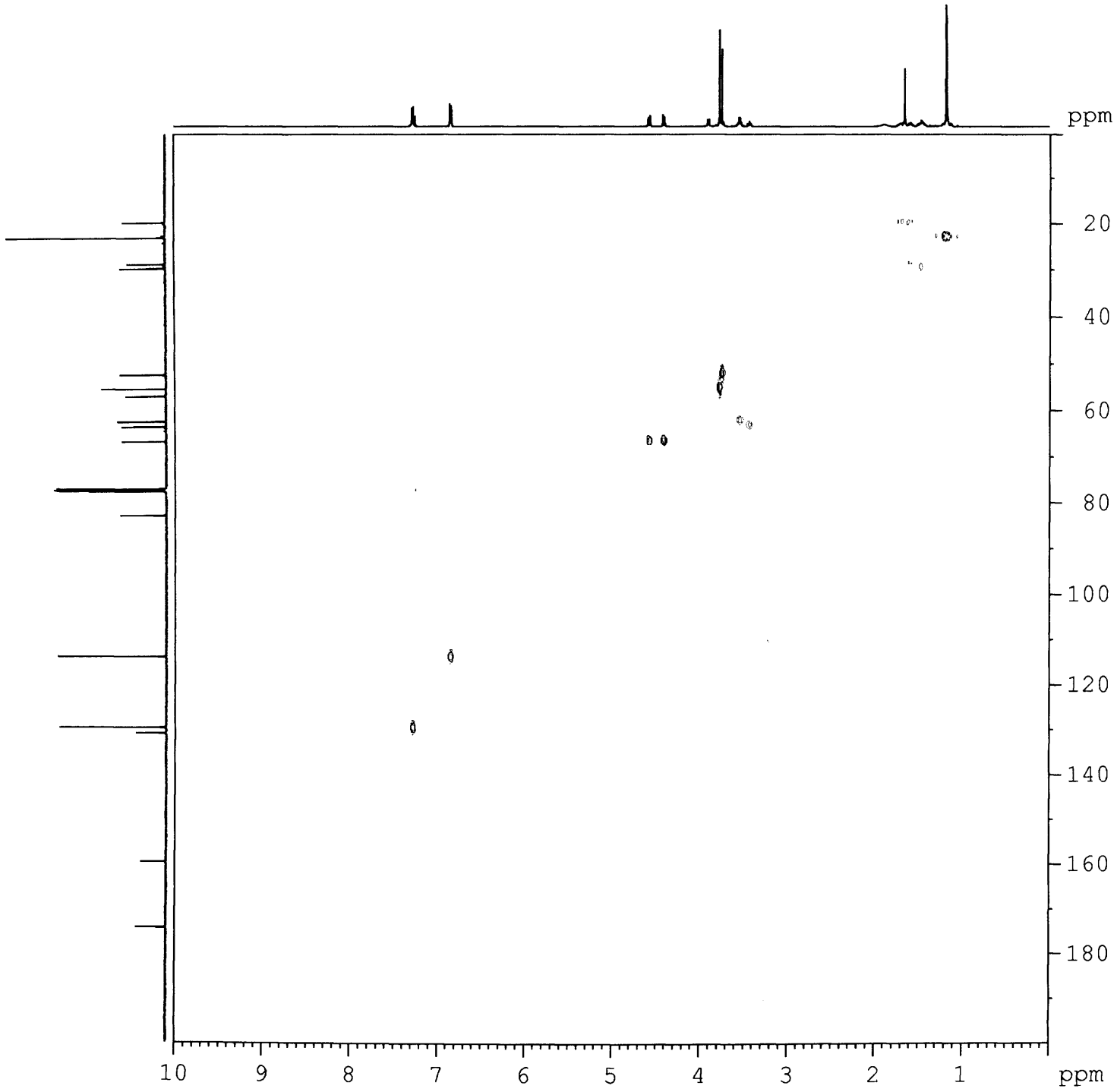




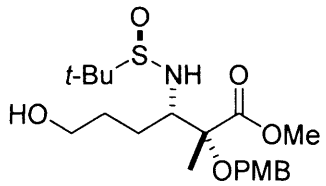


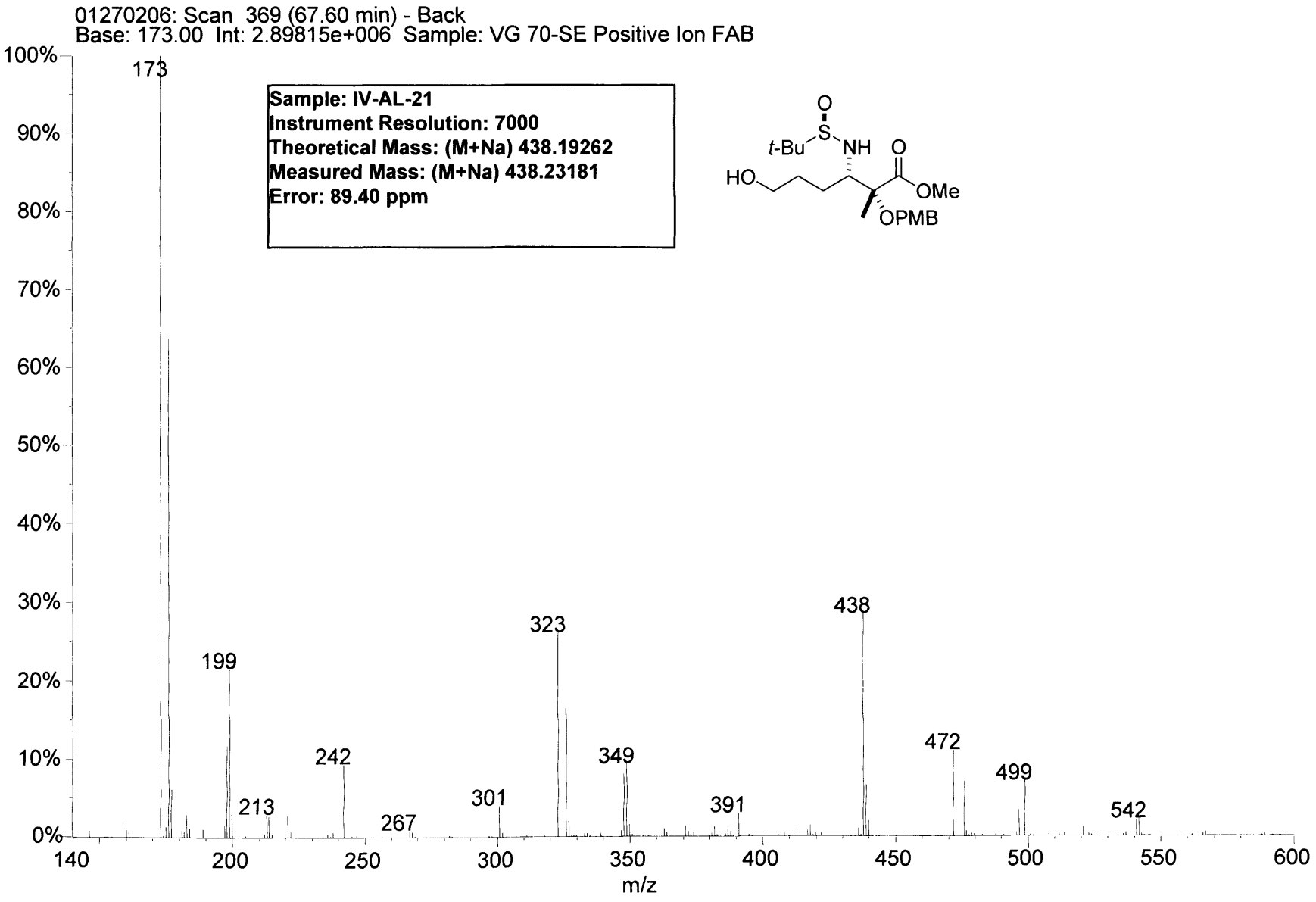
IV-AL-21
COSY
CDCl3 - 298K

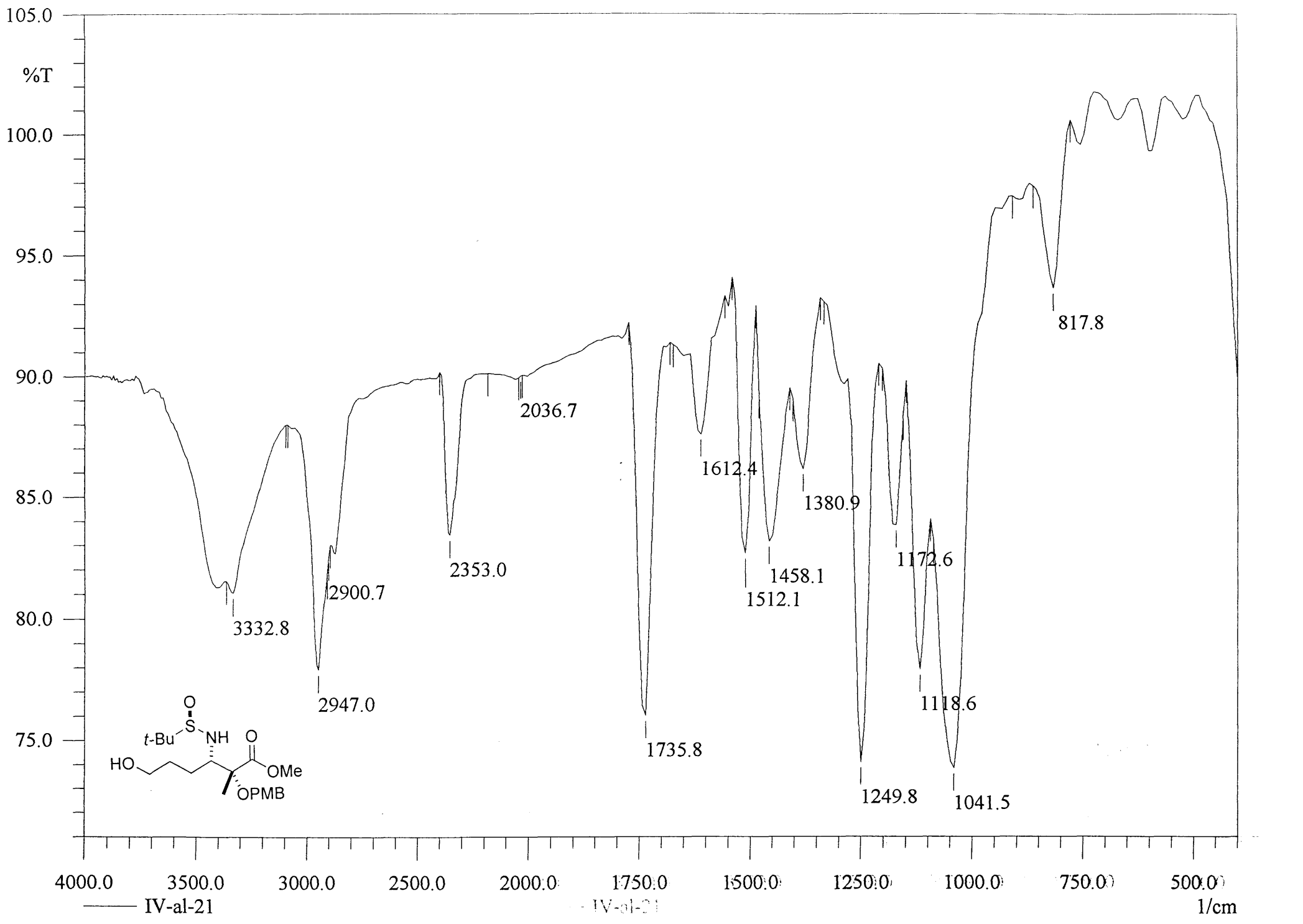


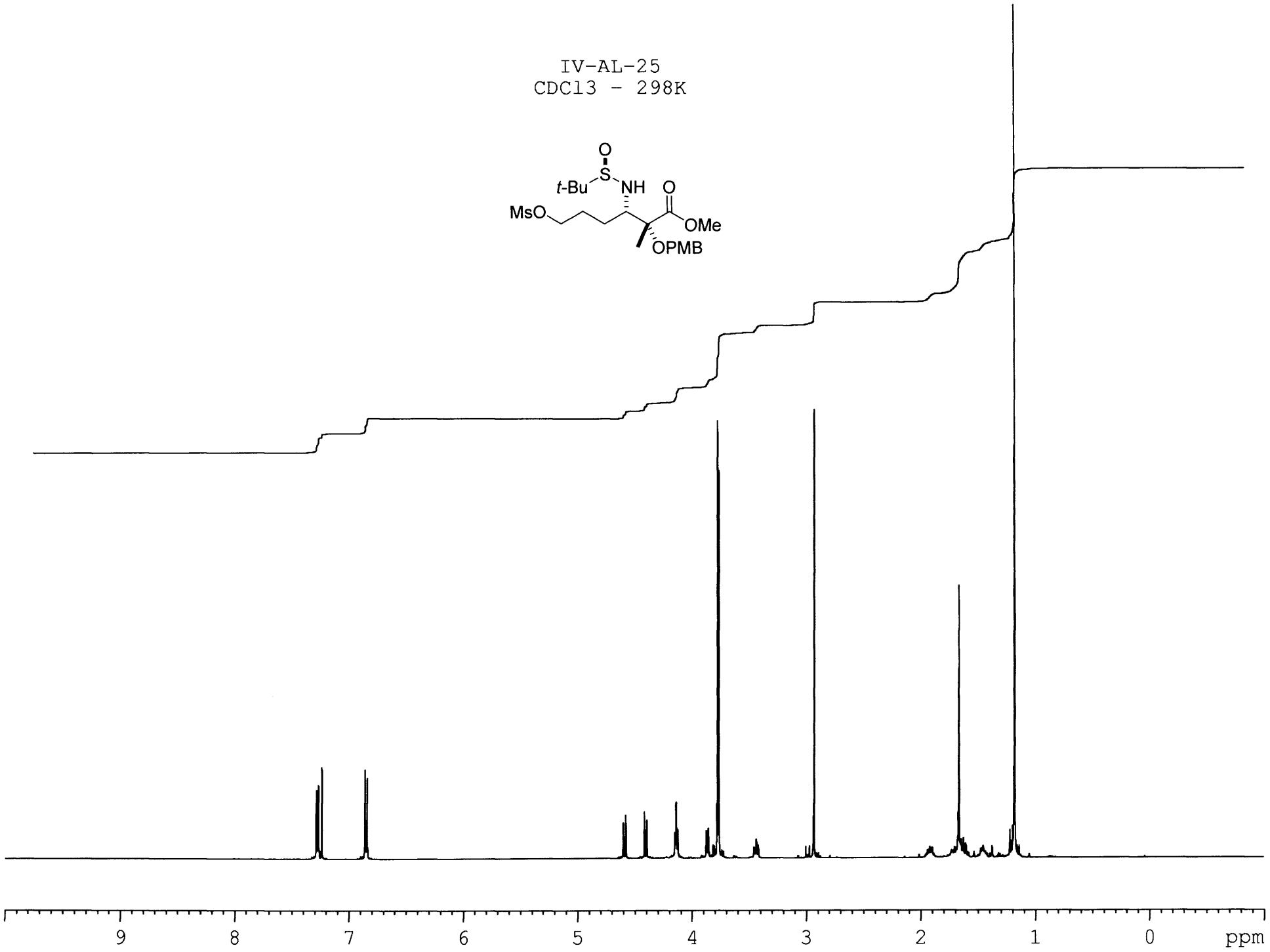


IV-AL-21
HMQC
CDCl3 - 298K

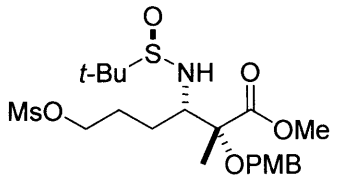



01270206: Scan 369 (67.60 min) - Back
Base: 173.00 Int: 2.89815e+006 Sample: VG 70-SE Positive Ion FAB
Sample: IV-AL-21
Instrument Resolution: 7000
Theoretical Mass: (M+Na) 438.19262
Measured Mass: (M+Na) 438.23181
Error: 89.40 ppm
O
S
t-Bu
NH
O
HO
OMe
OPMB
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
173
199
213
242
267
301
323
349
391
438
472
499
542
140
200
250
300
350
400
450
500
550
600
m/z

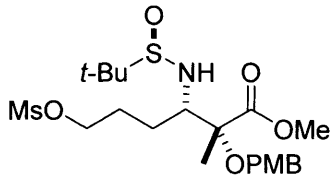

105.0
%T
100.0
95.0
90.0
85.0
80.0
75.0
3332.8
2900.7
2947.0
2353.0
2036.7
1735.8
1612.4
1512.1
1458.1
1380.9
1249.8
1172.6
1118.6
1041.5
817.8
O
S
t-Bu
NH
O
HO
OMe
OPMB
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
IV-al-21
1/cm

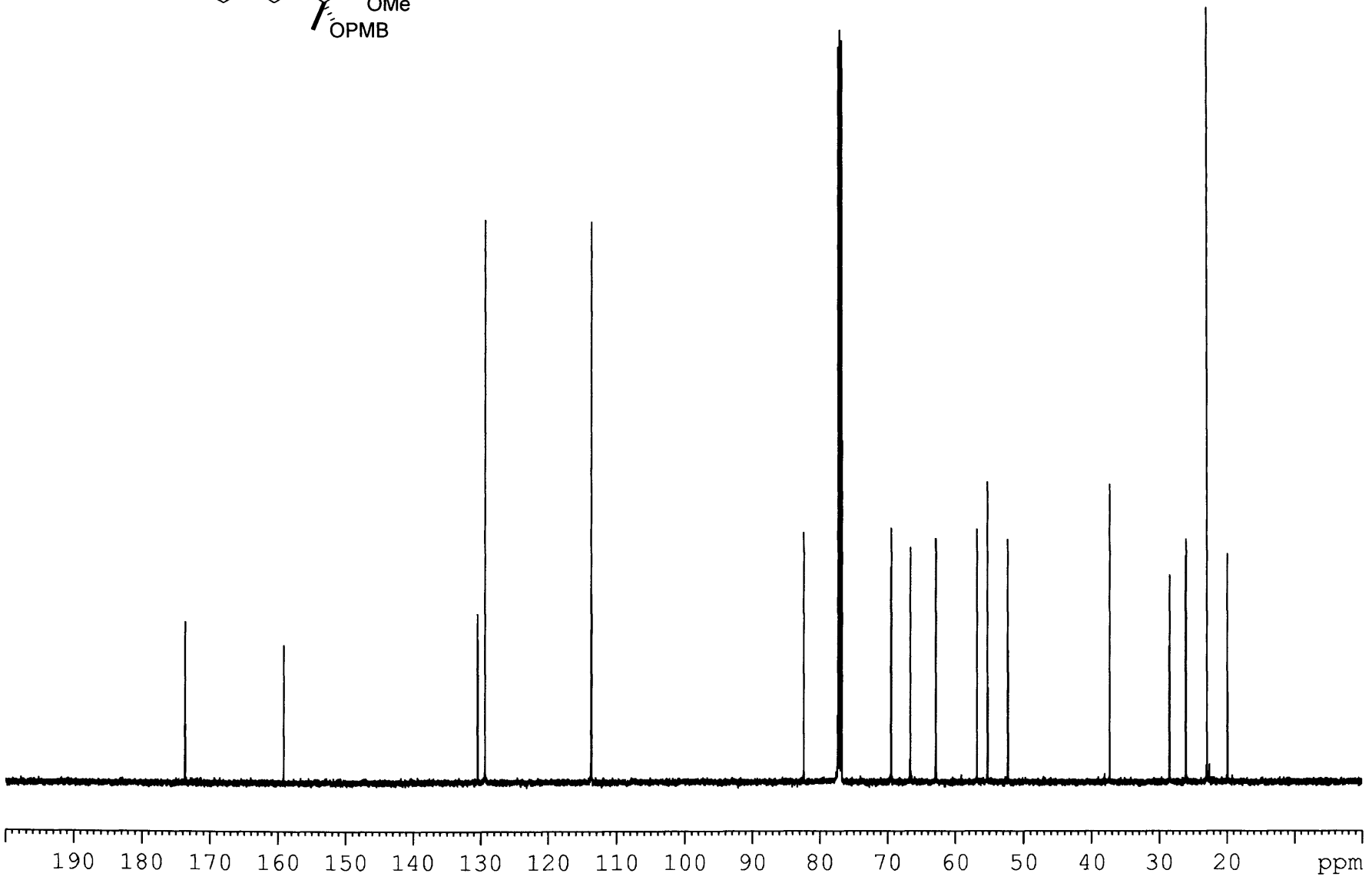

IV-AL-25
CDCl3 - 298K
O
S
t-Bu
NH
O
MsO
OMe
OPMB
9
8
7
6
5
4
3
2
1
0
ppm

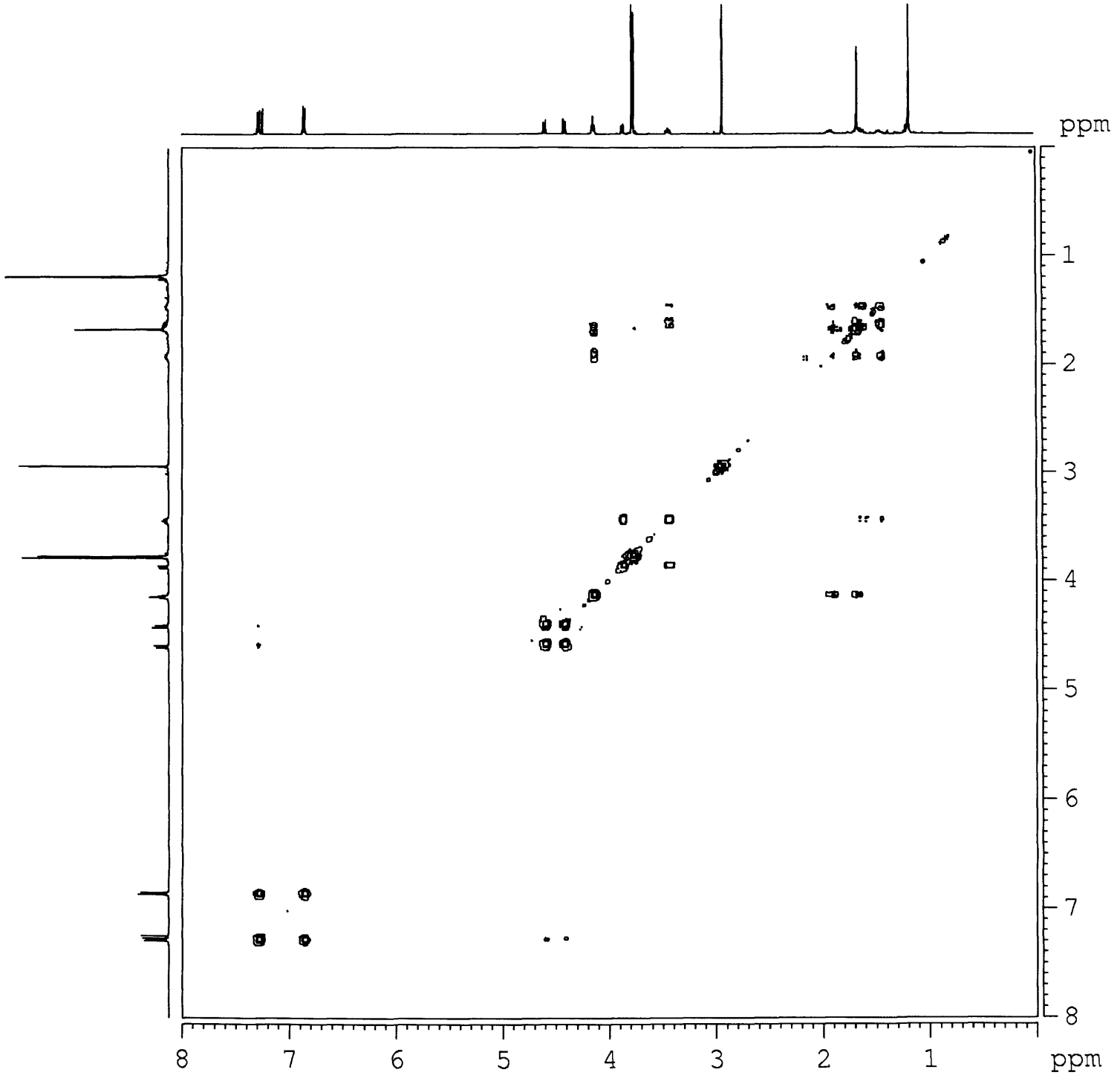
IV-AL-25
DEPT
CDCl3 - 298K



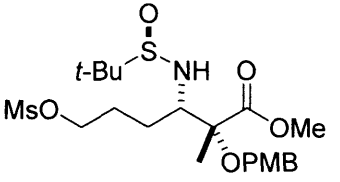
IV-AL-25
13C
CDCl3 - 298K

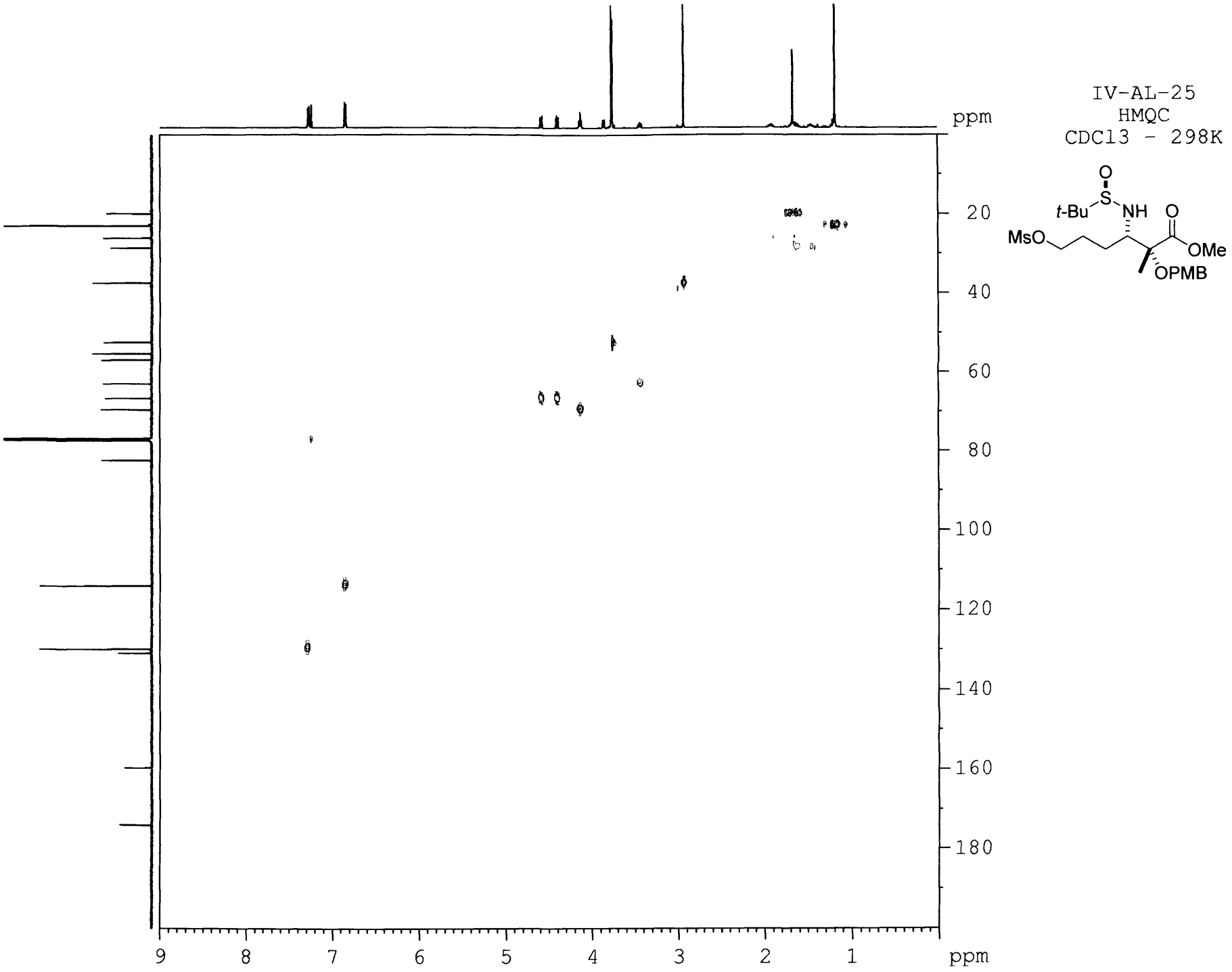


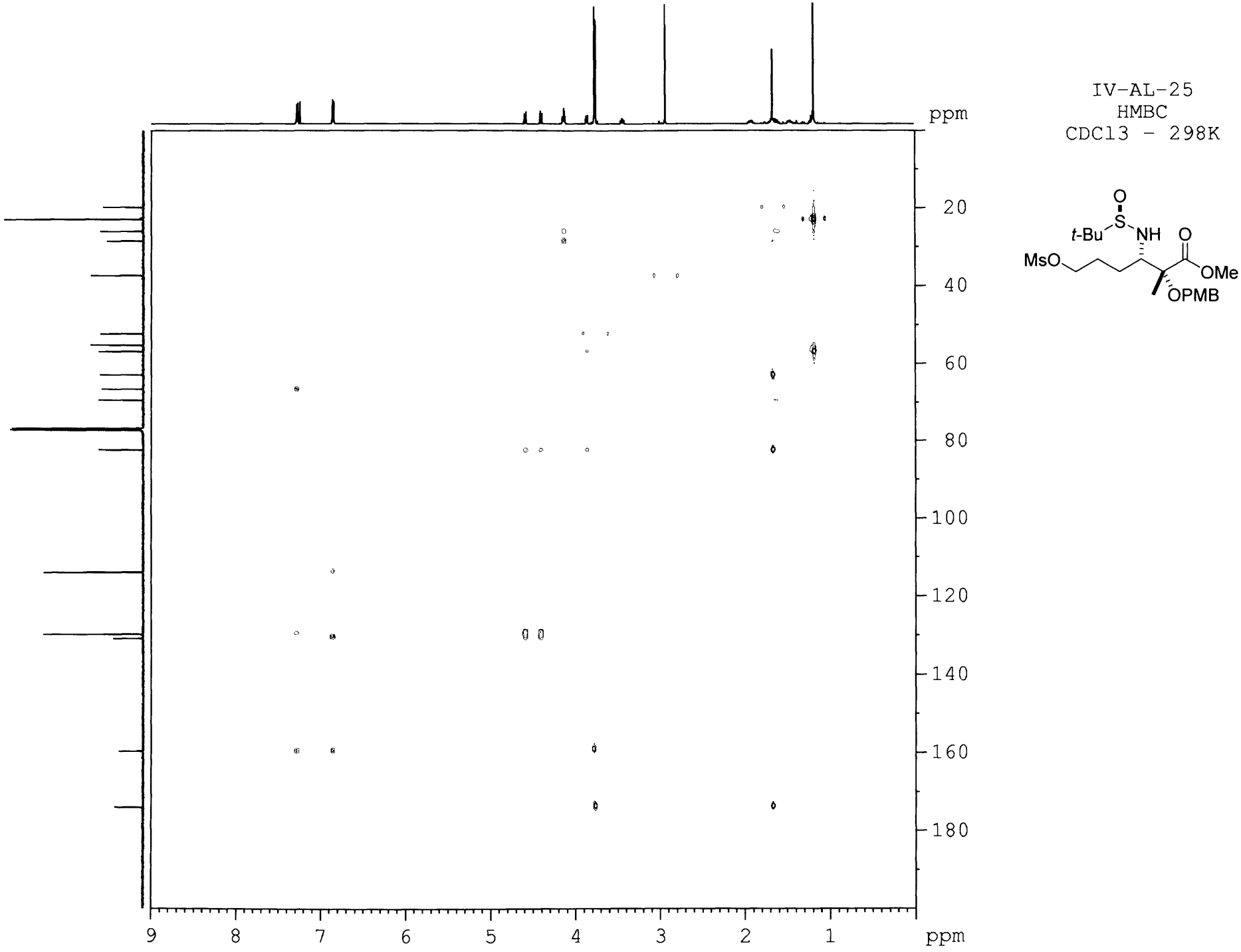




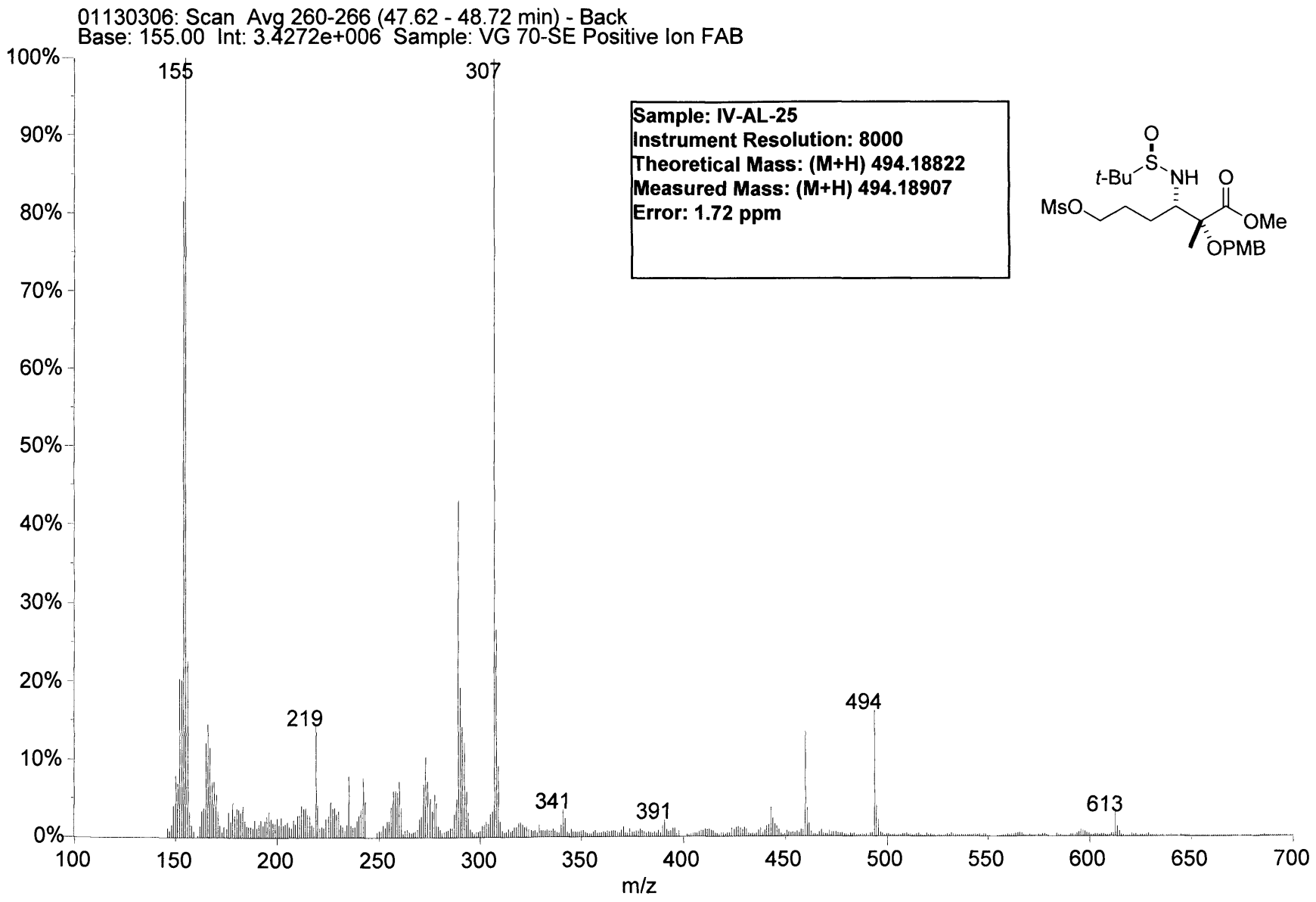
IV-AL-25
COSY
CDCl3 - 298K

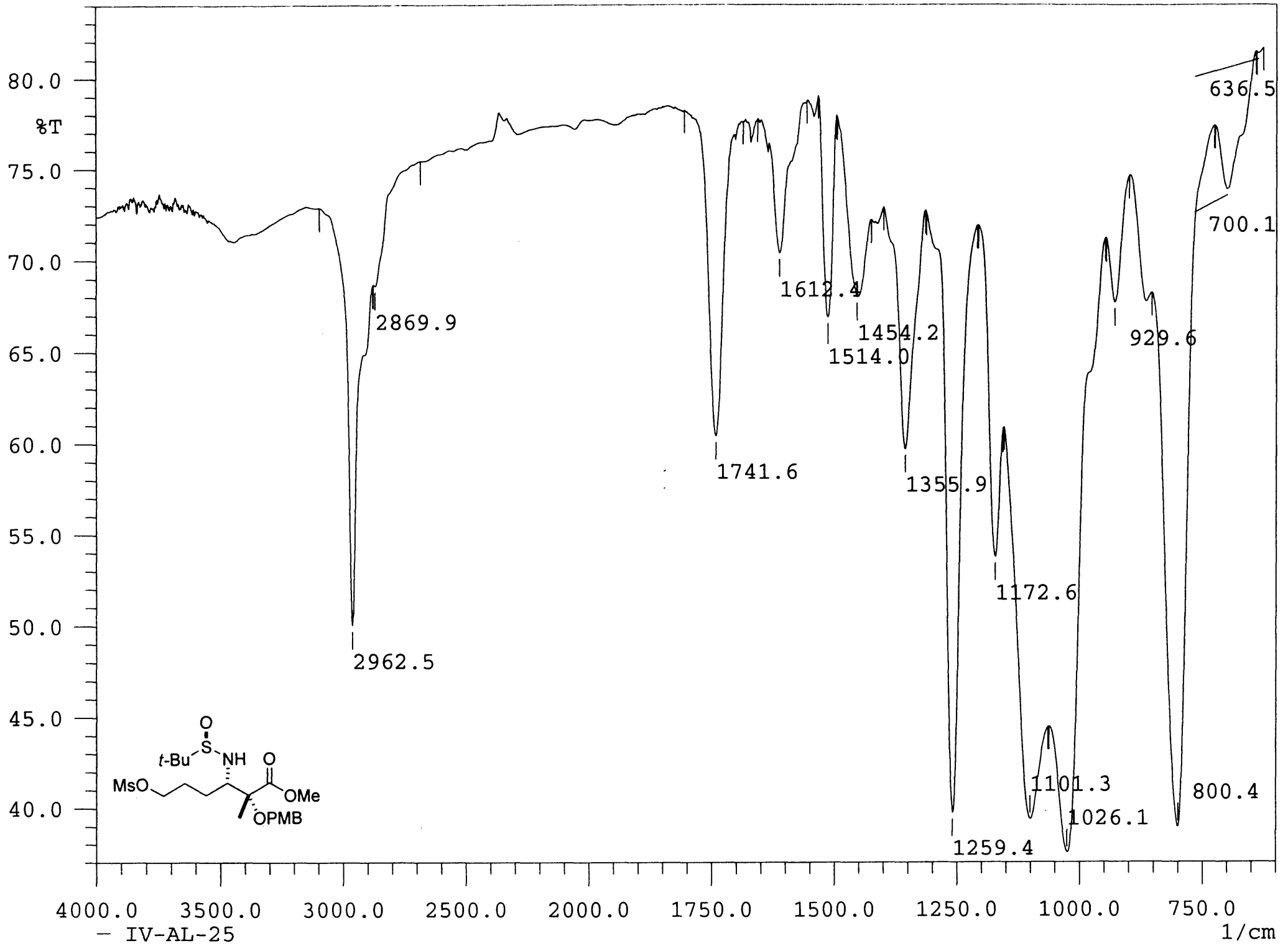


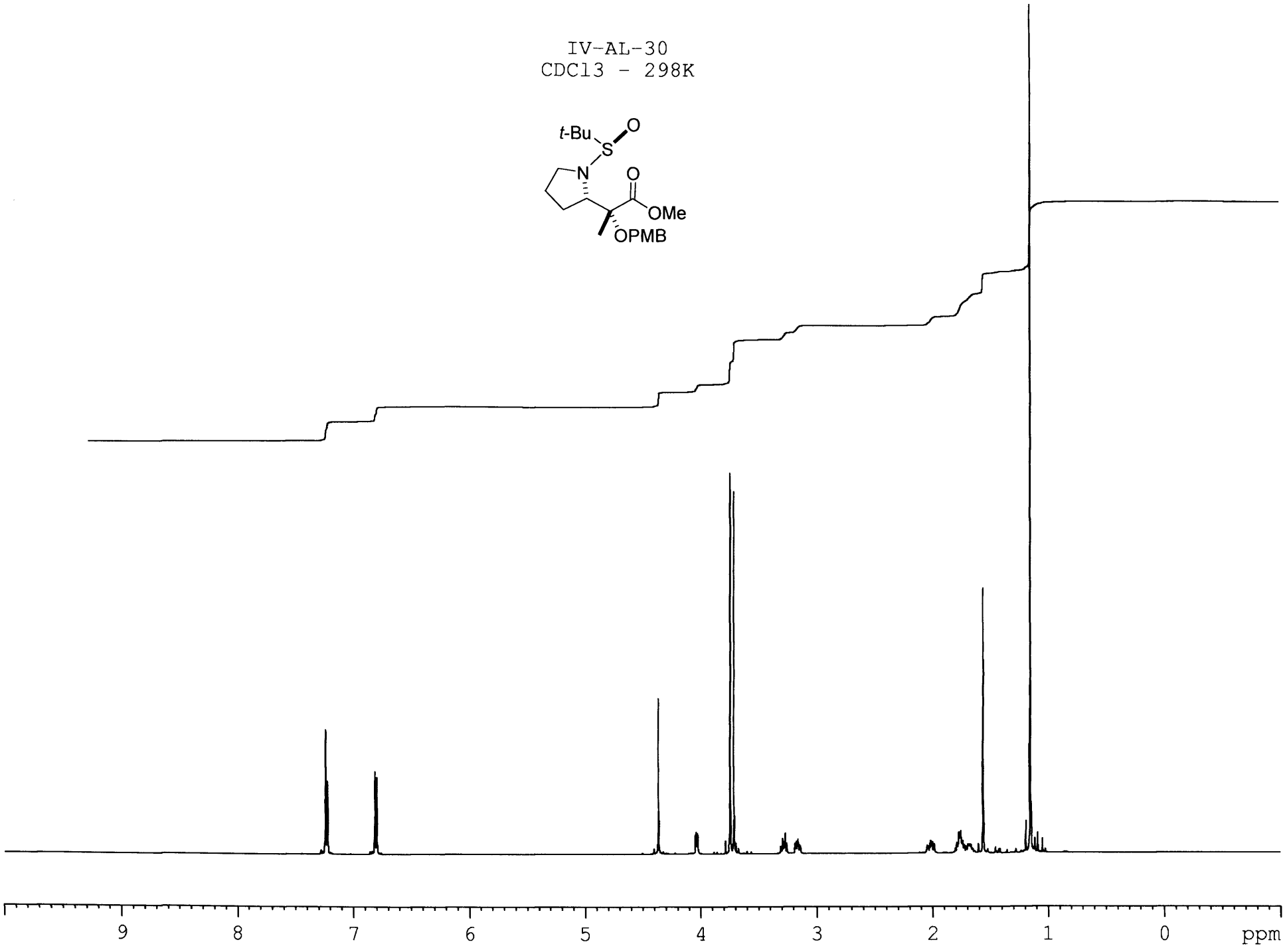

IV-AL-25
HMQC
CDCl3 - 298K
ppm
20
40
60
80
100
120
140
160
180
9
8
7
6
5
4
3
2
1
ppm
O
S
t-Bu
NH
O
MsO
OMe
OPMB



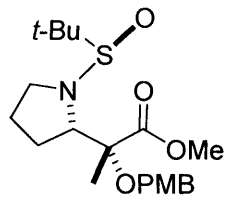
IV-AL-25
HMBC
CDCl3 - 298K


01130306: Scan Avg 260-266 (47.62 - 48.72 min) - Back
Base: 155.00 Int: 3.4272e+006 Sample: VG 70-SE Positive Ion FAB
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
155
307
219
341
391
494
613
100
150
200
250
300
350
400
450
500
550
600
650
700
m/z
Sample: IV-AL-25
Instrument Resolution: 8000
Theoretical Mass: (M+H) 494.18822
Measured Mass: (M+H) 494.18907
Error: 1.72 ppm
O
S
t-Bu
NH
O
MsO
OMe
OPMB

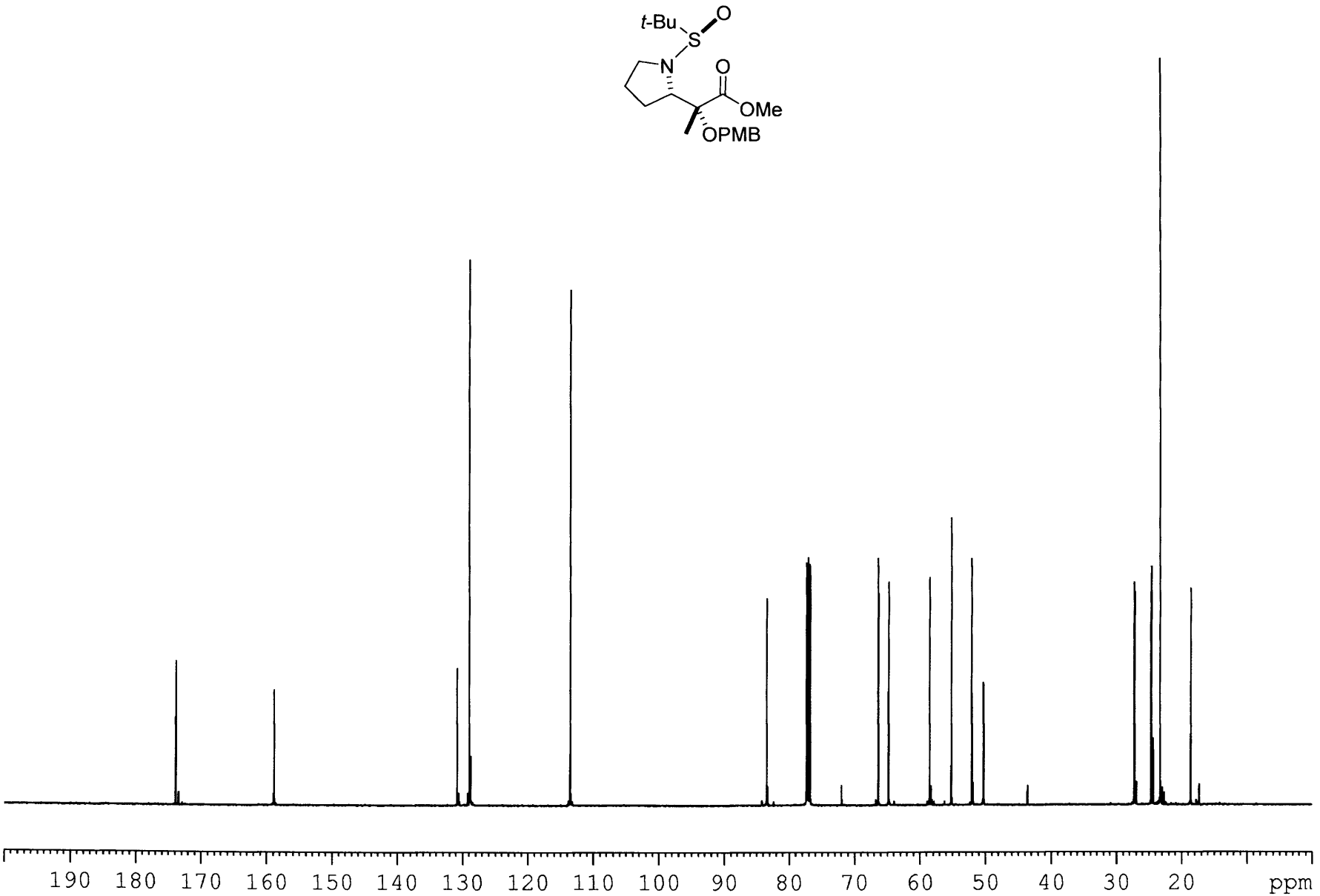

80.0
%T
75.0
70.0
65.0
60.0
55.0
50.0
45.0
40.0
2869.9
2962.5
1741.6
1612.4
1514.0
1454.2
1355.9
1259.4
1172.6
1101.3
1026.1
929.6
800.4
700.1
636.5
t-Bu
S
NH
O
MsO
OMe
OPMB
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
1/cm
- IV-AL-25

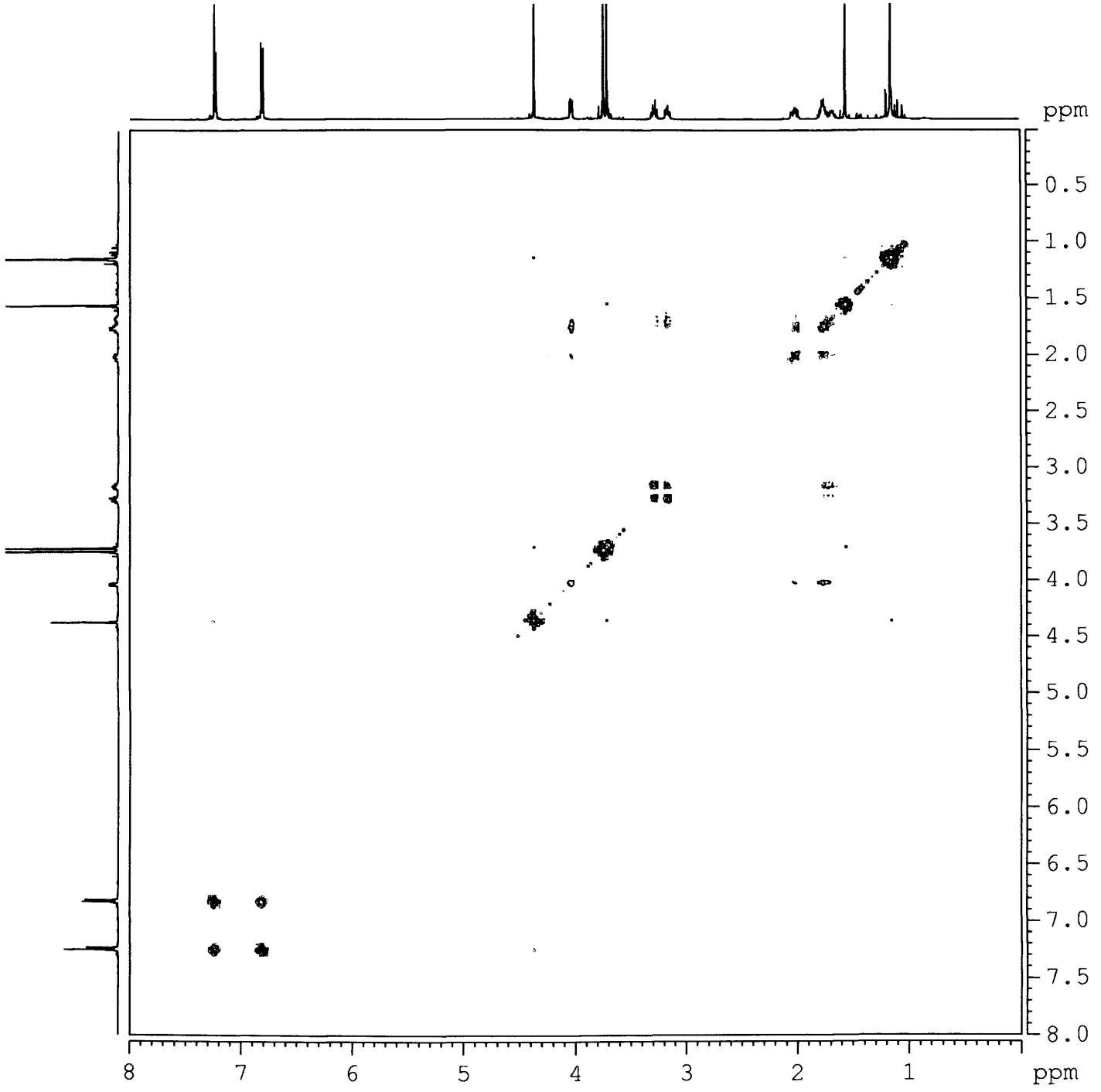

IV-AL-30
CDCl3 - 298K
t-Bu
S
O
N
O
OMe
OPMB
9
8
7
6
5
4
3
2
1
0
ppm

IV-AL-30
dept
CDCl3 - 298K

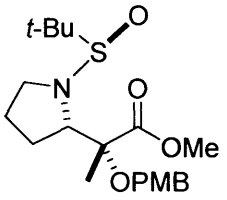


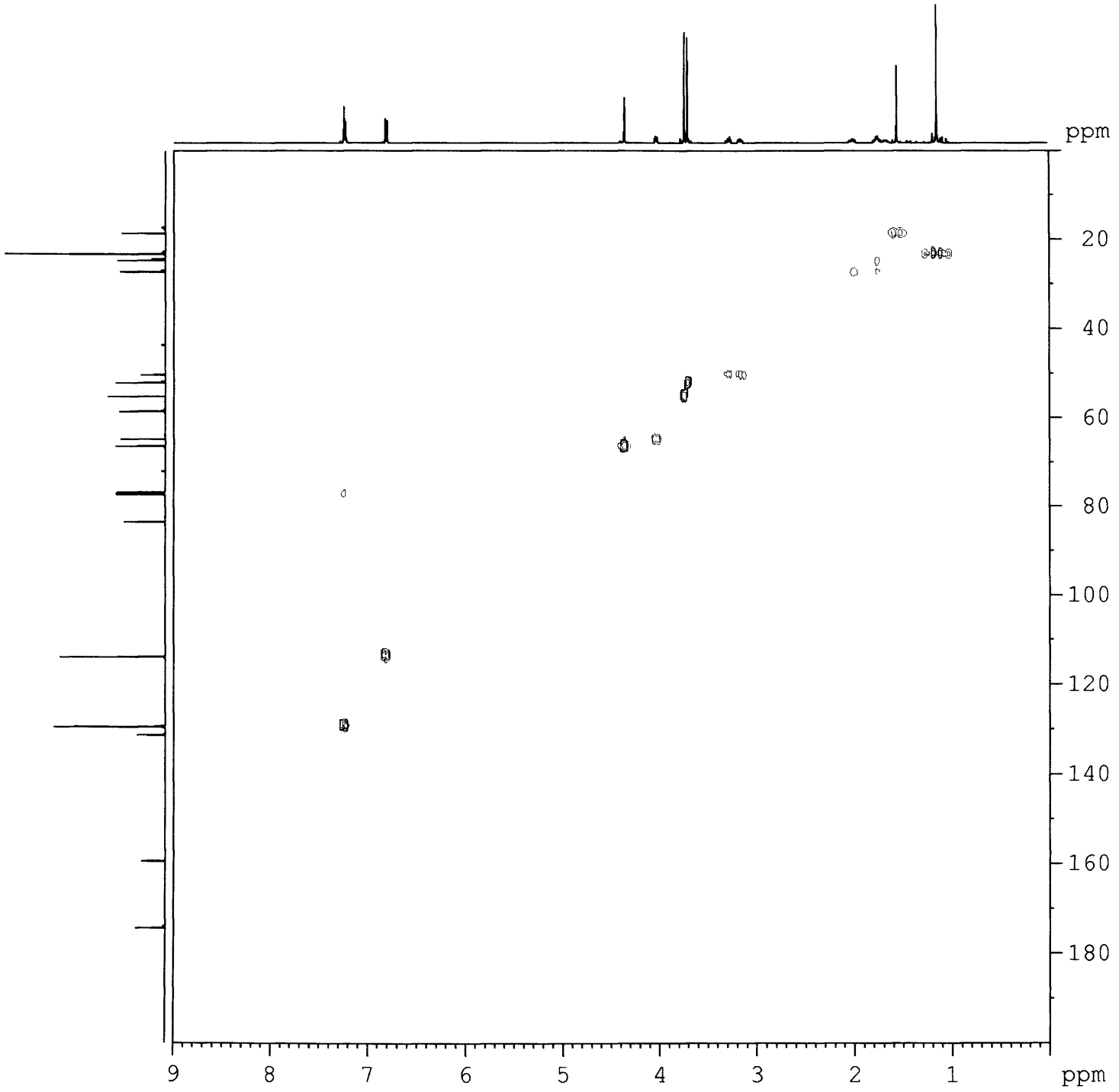
IV-AL-30
CDCl3 - 298K



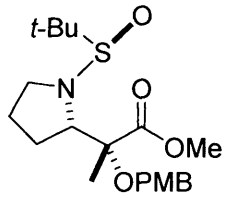


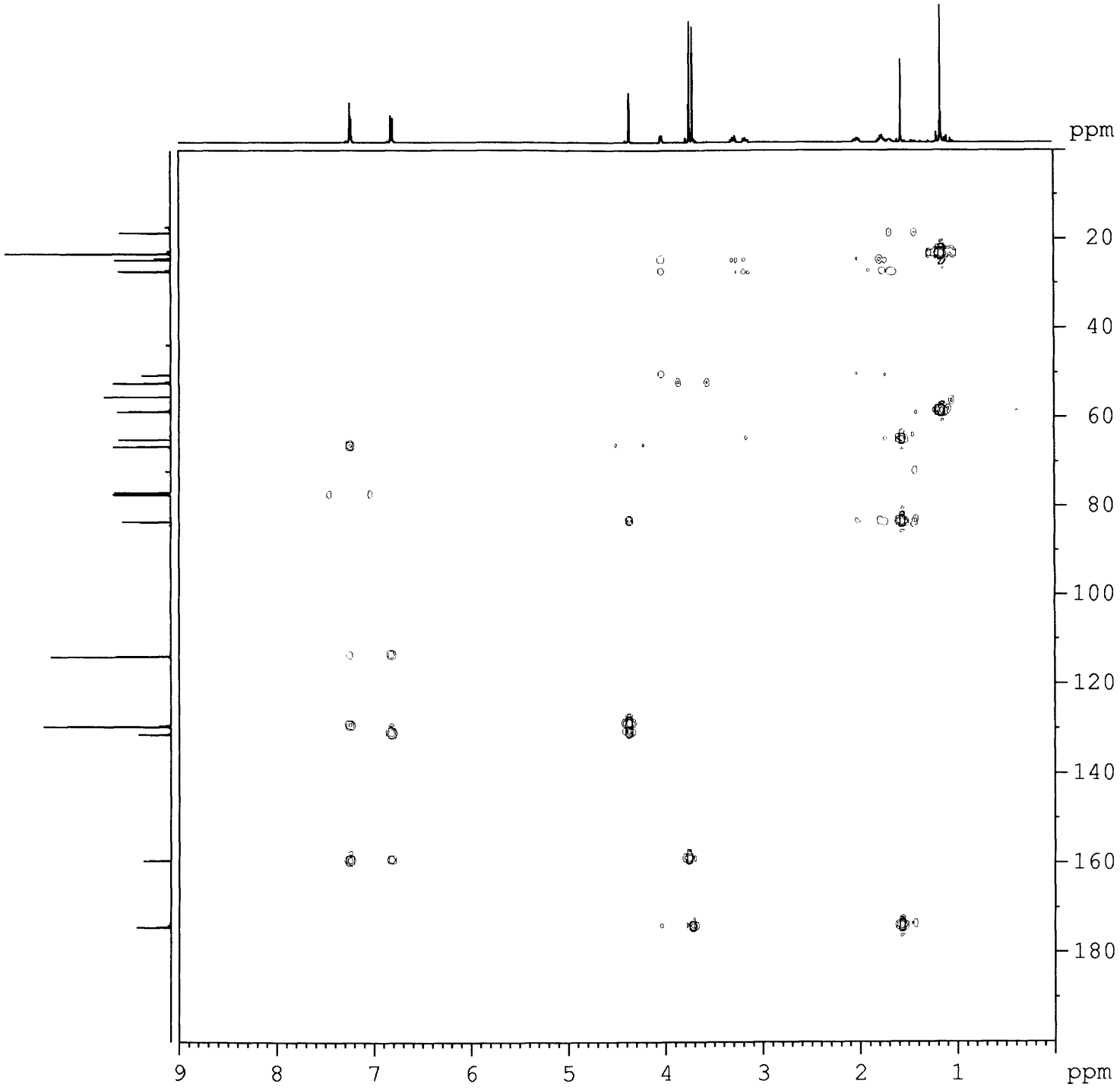
IV-AL-30
COSY
CDCl3 - 298K



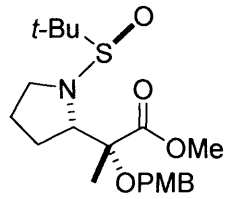


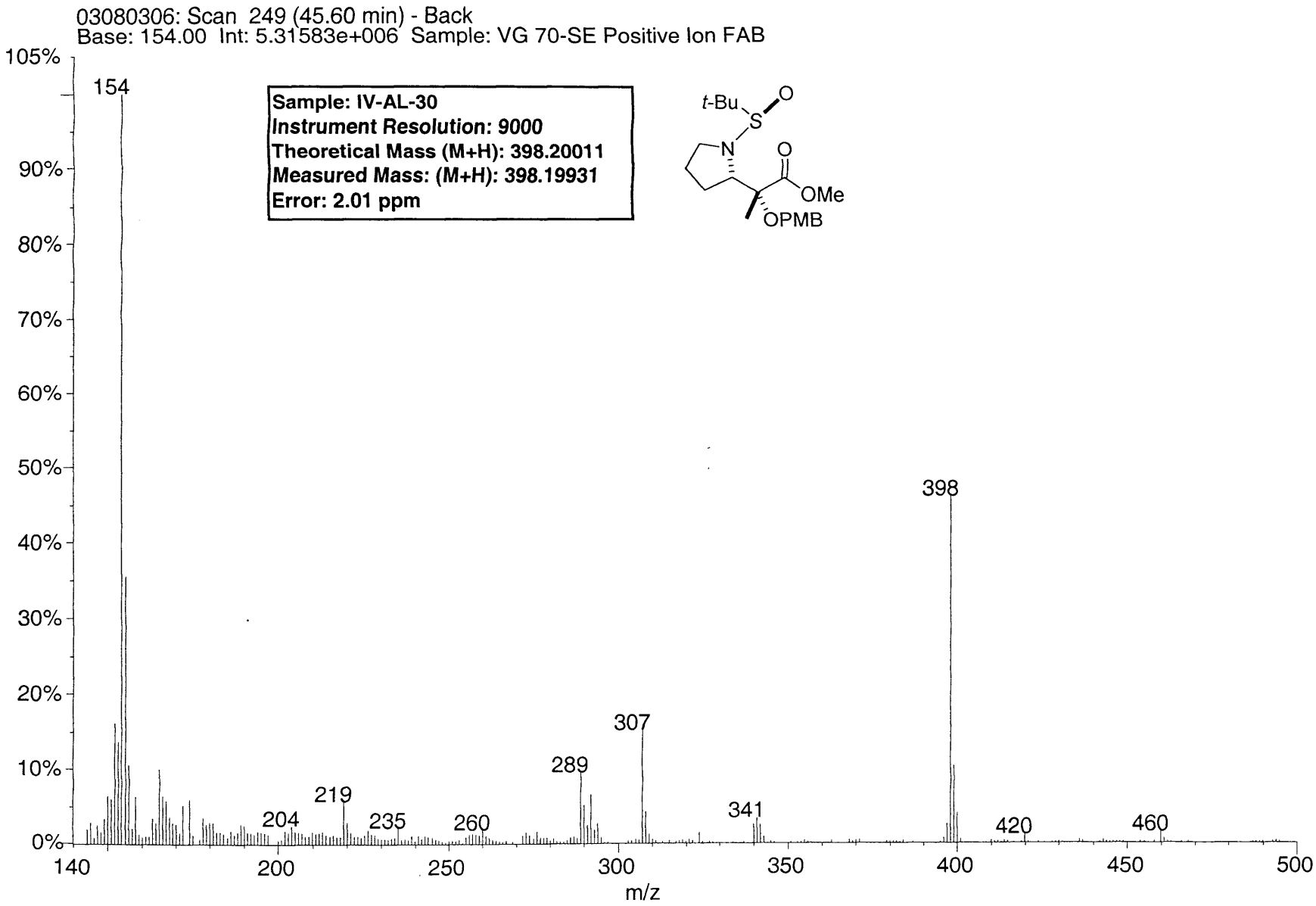
IV-AL-30
HMQC
CDCl3 - 298K

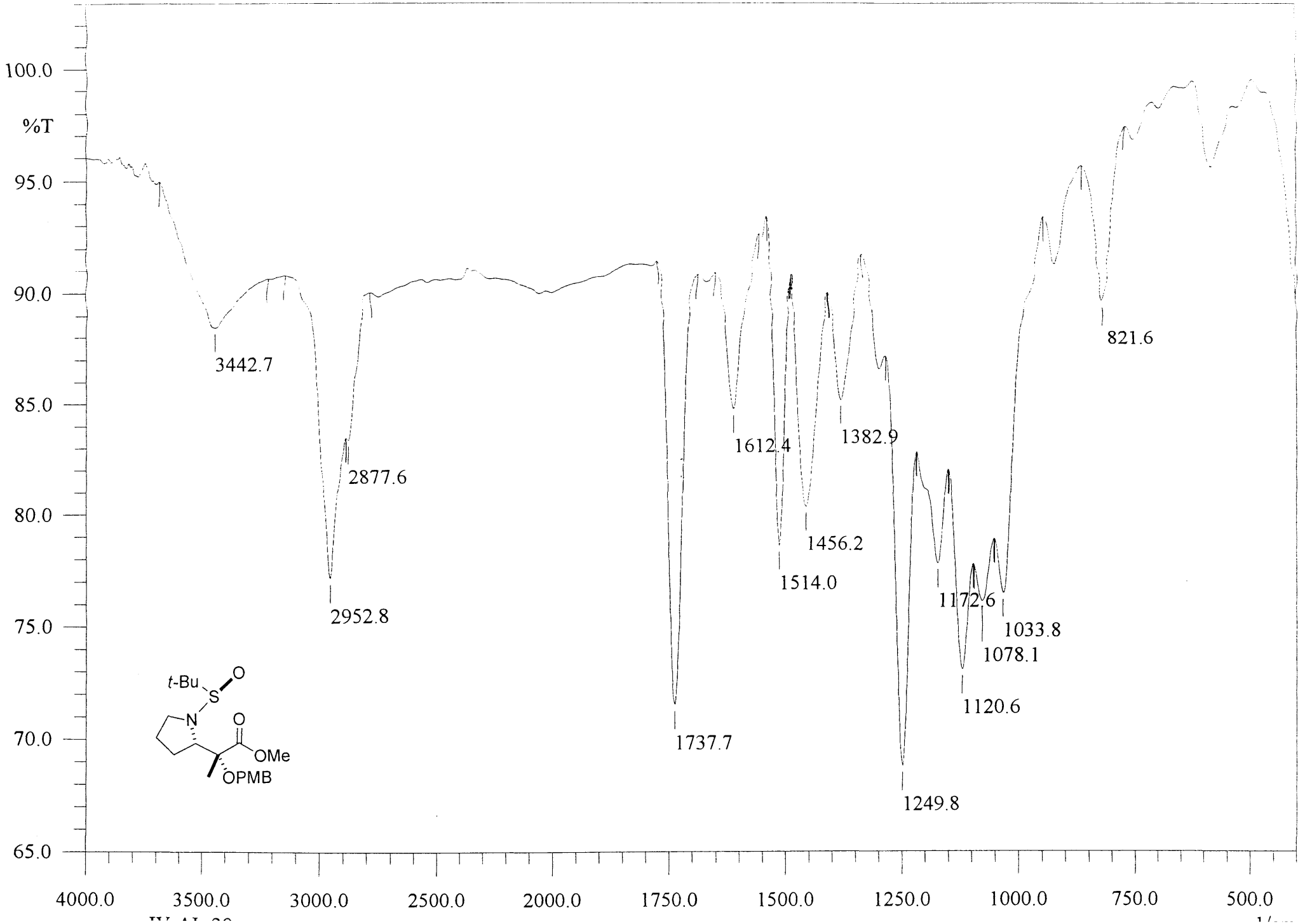


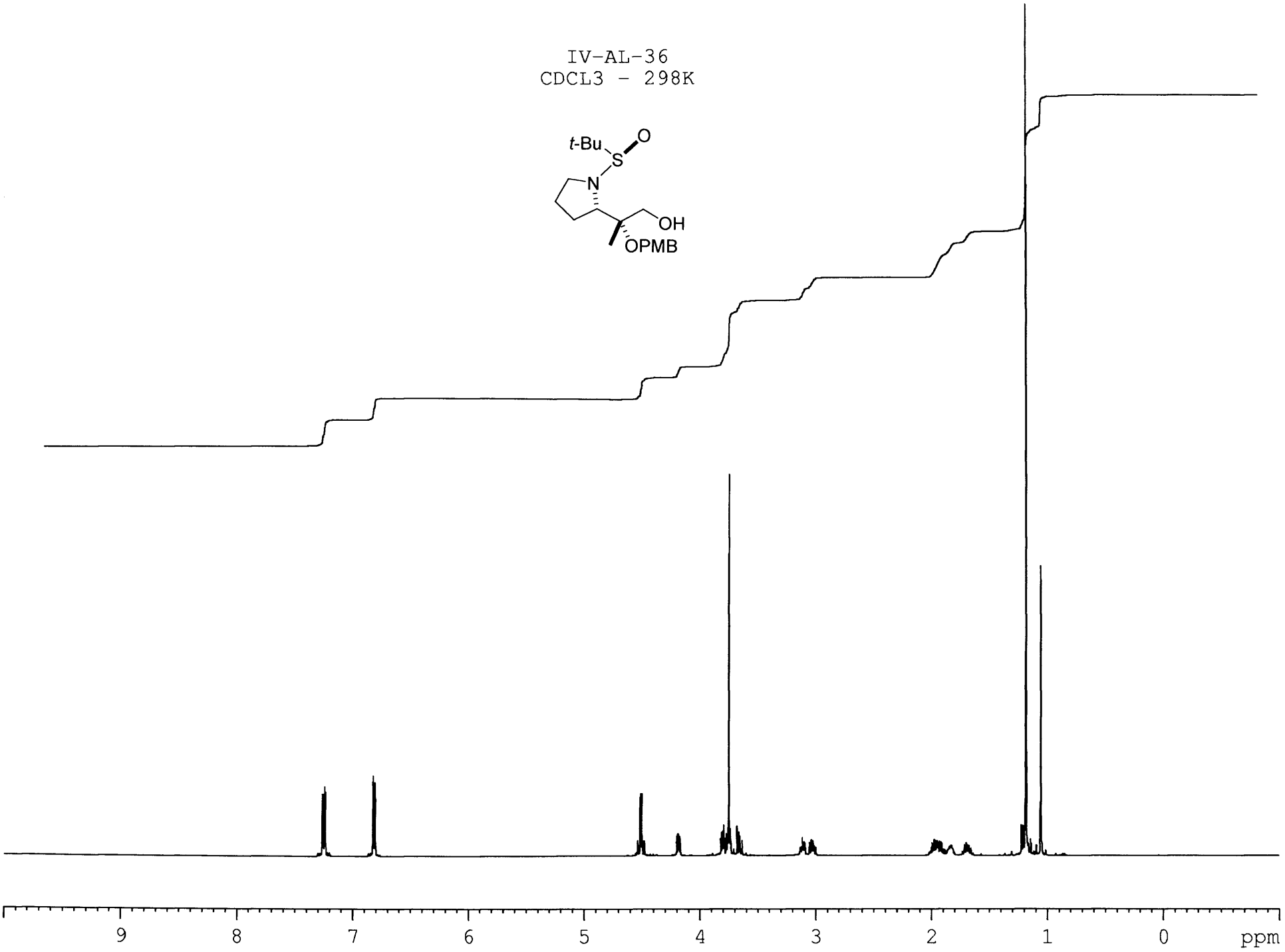


IV-AL-30
HMBC
CDCl3 - 298K

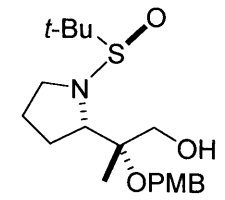



03080306: Scan 249 (45.60 min) - Back
Base: 154.00 Int: 5.31583e+006 Sample: VG 70-SE Positive Ion FAB
Sample: IV-AL-30
Instrument Resolution: 9000
Theoretical Mass (M+H): 398.20011
Measured Mass: (M+H): 398.19931
Error: 2.01 ppm
t-Bu
S
O
N
O
OMe
OPMB
105%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
154
398
307
289
219
204
235
260
341
420
460
140
200
250
300
350
400
450
500
m/z

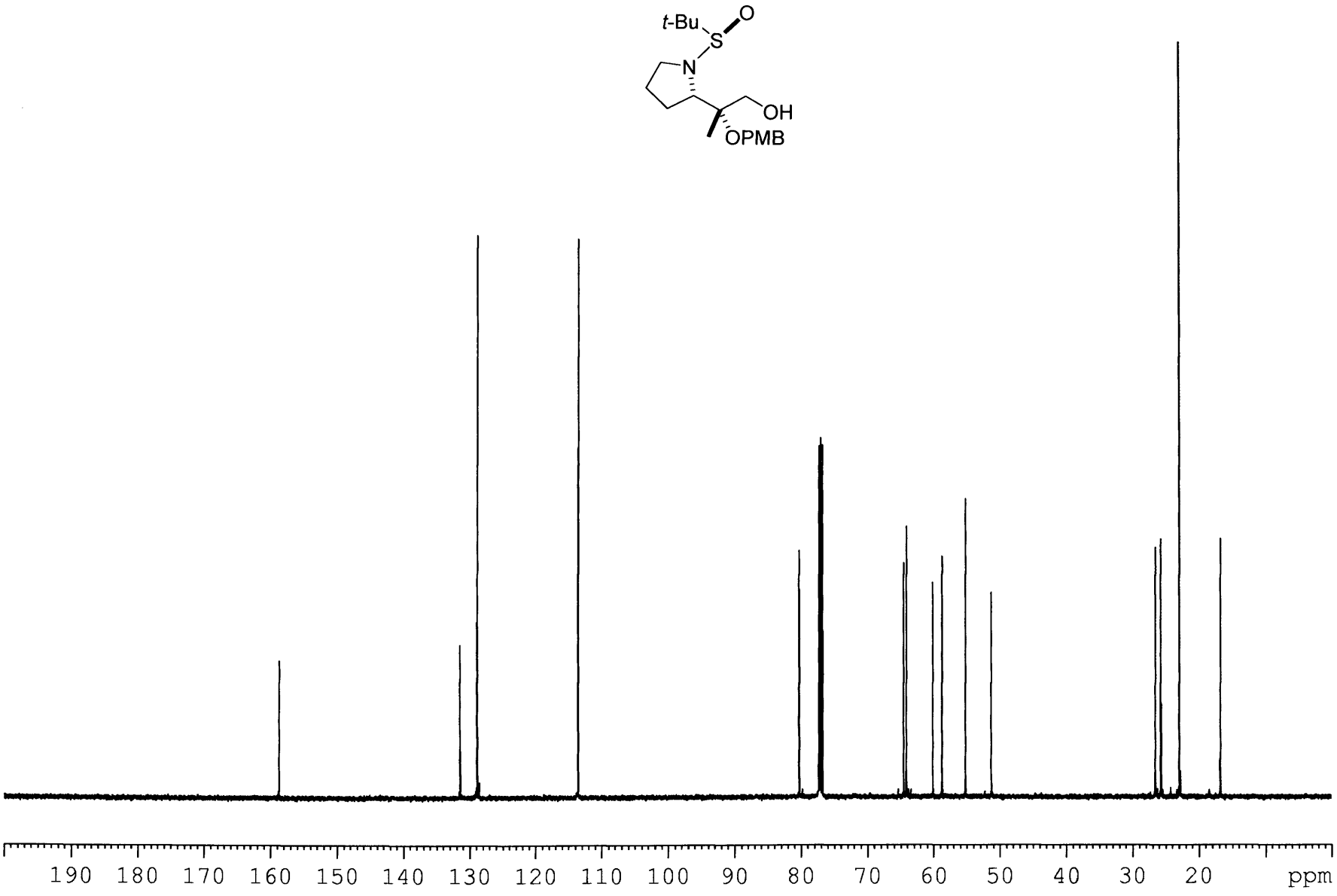

100.0
%T
95.0
90.0
85.0
80.0
75.0
70.0
65.0
3442.7
2877.6
2952.8
1737.7
1612.4
1382.9
1514.0
1456.2
1172.6
1033.8
1078.1
1120.6
1249.8
821.6
t-Bu
S
O
N
O
OMe
OPMB
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0

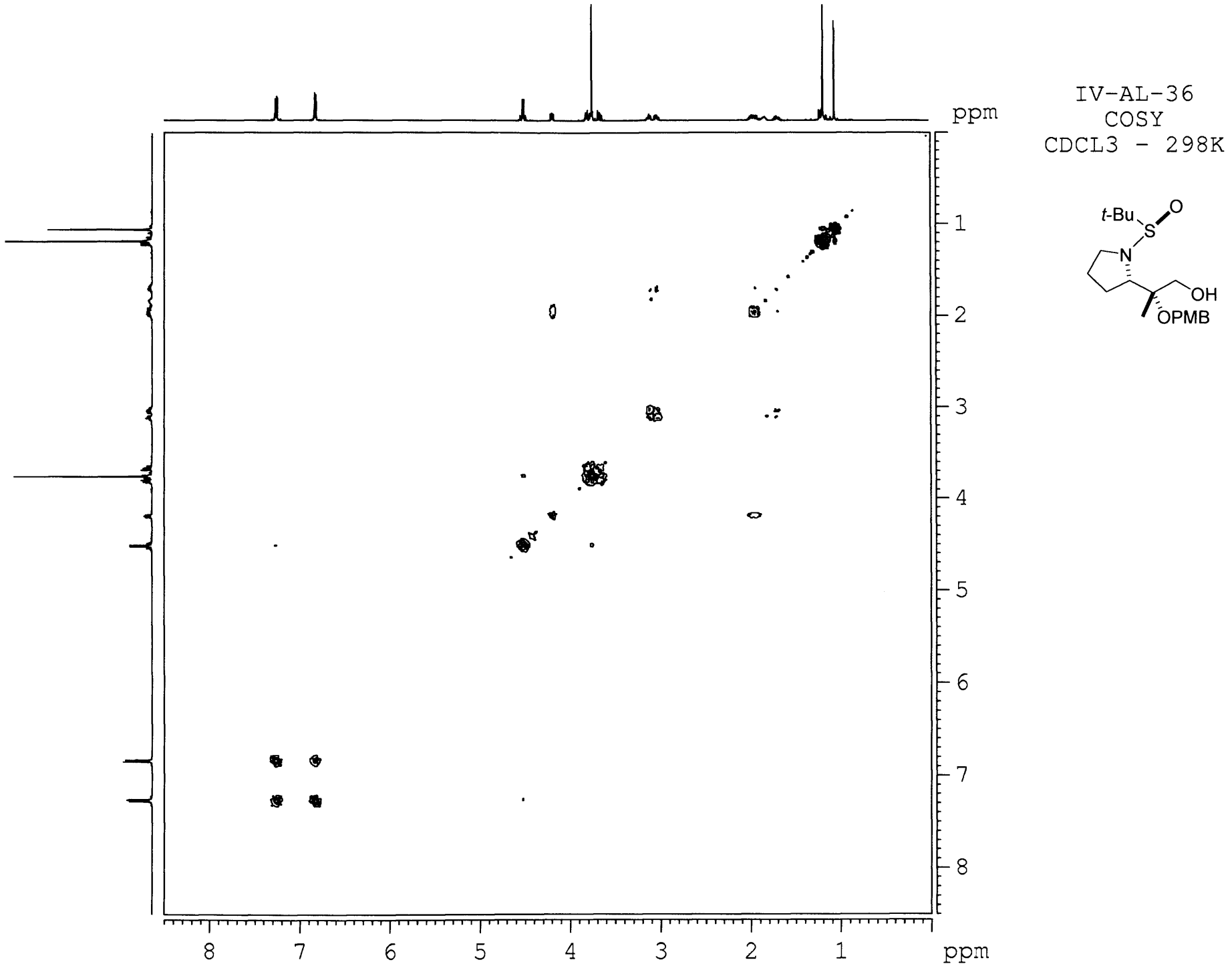

IV-AL-36
CDCL3 - 298K
t-Bu
S
O
N
OH
OPMB
9
8
7
6
5
4
3
2
1
0
ppm

IV-AL-36
DEPT
CDCL3 - 298K

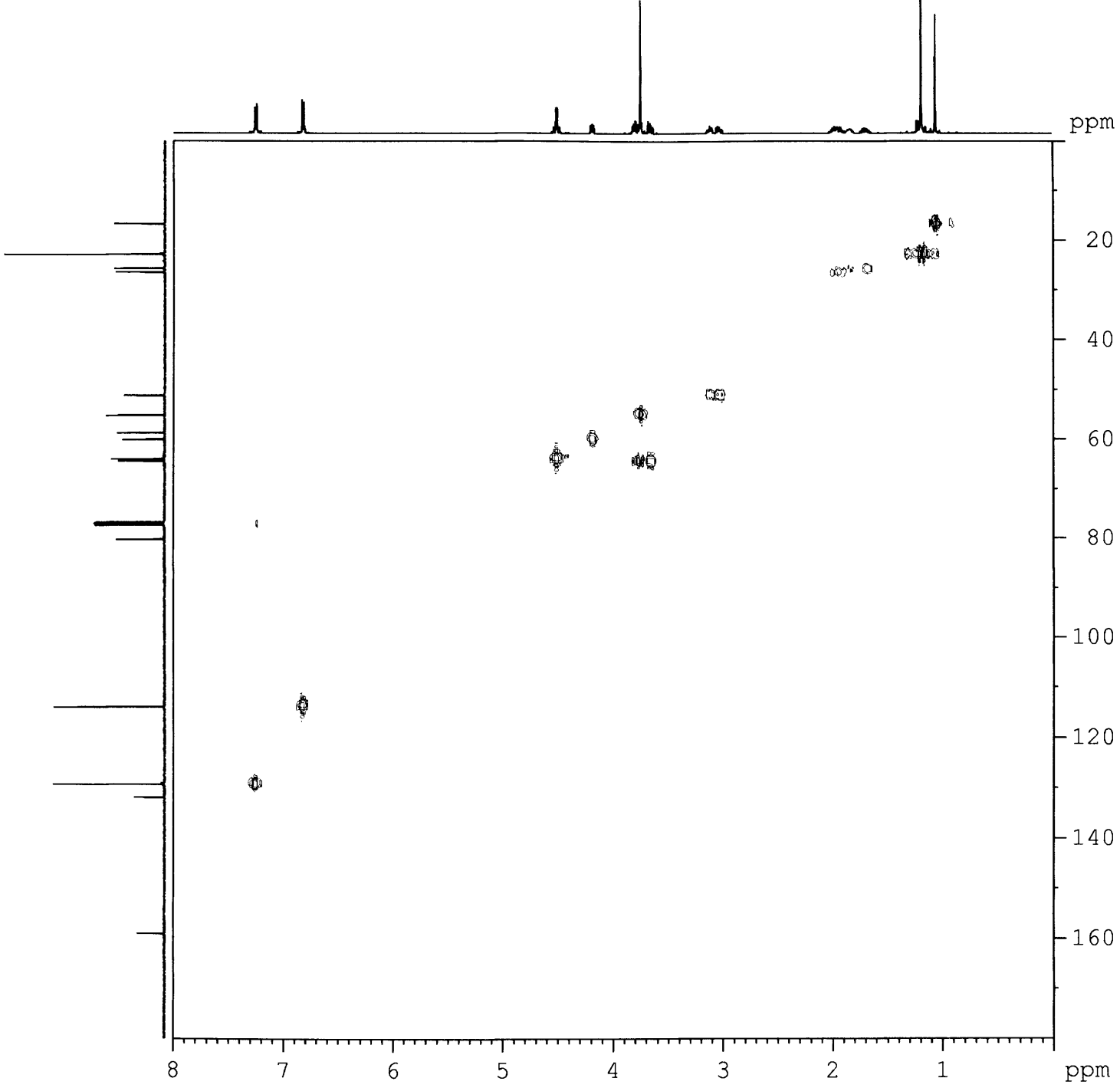


IV-AL-36
13C
CDCL3 - 298K

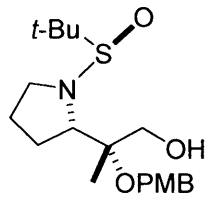


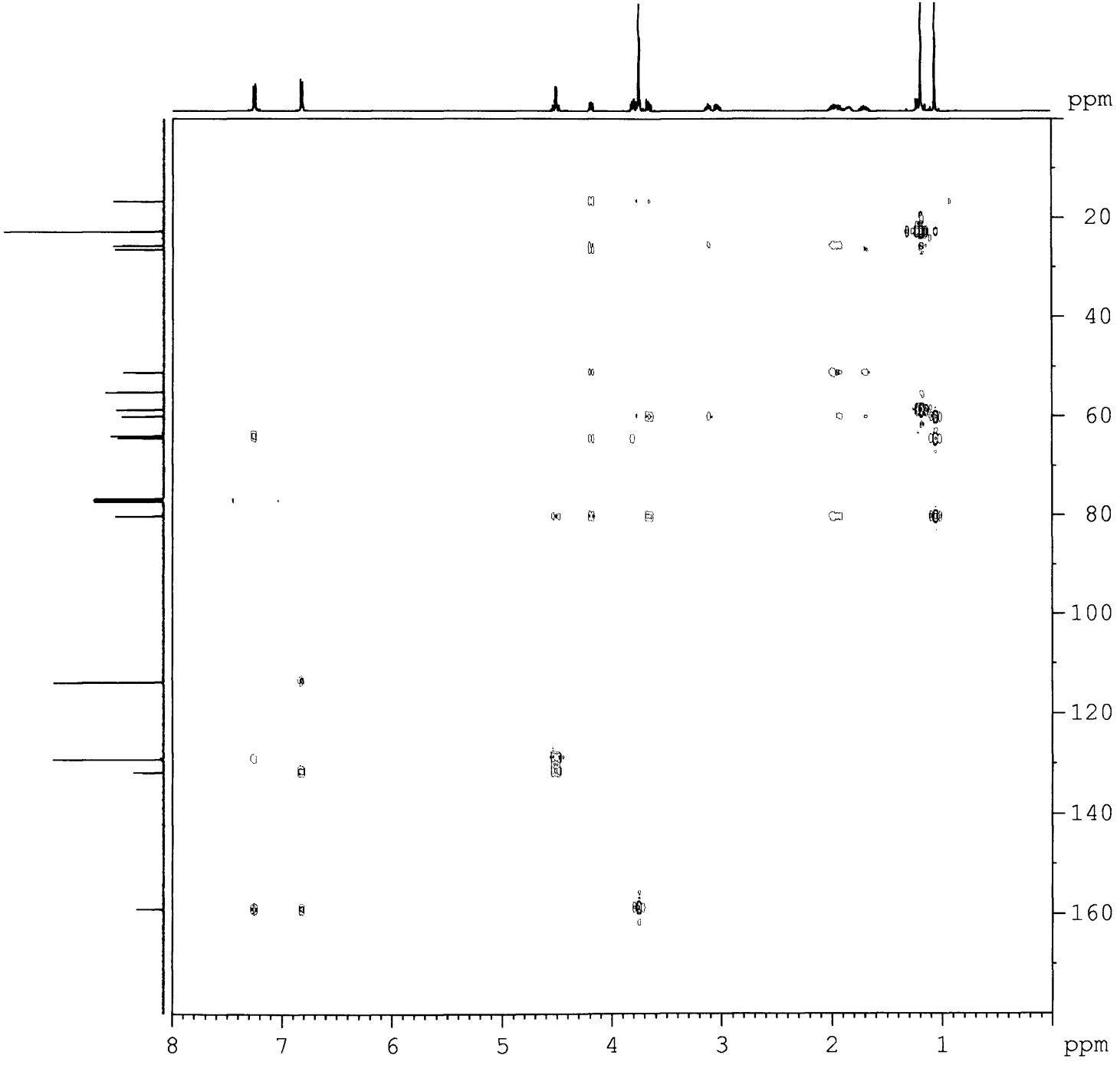


IV-AL-36
COSY
CDCL3 - 298K

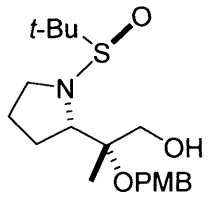


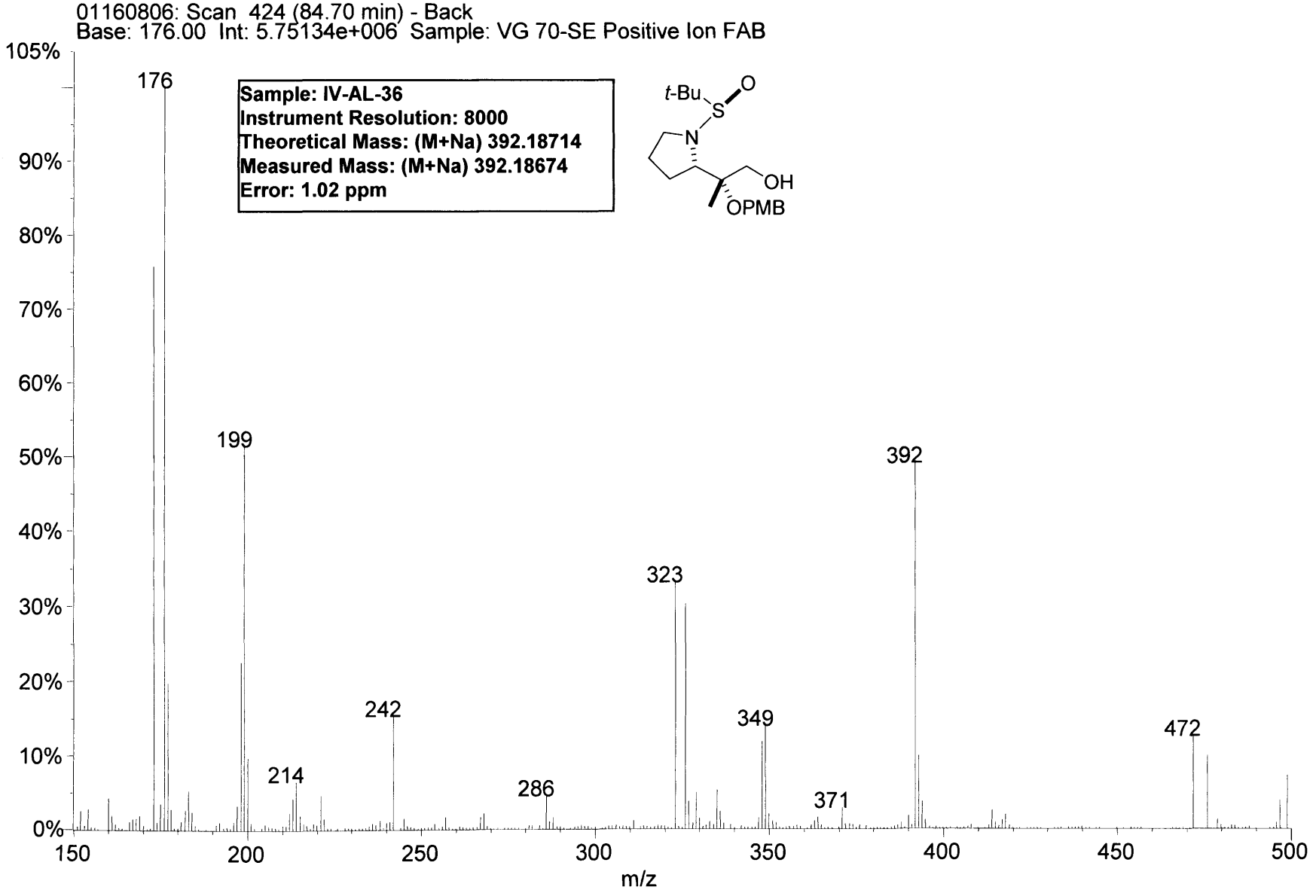
IV-AL-36
HMQC
CDCL3 - 298K

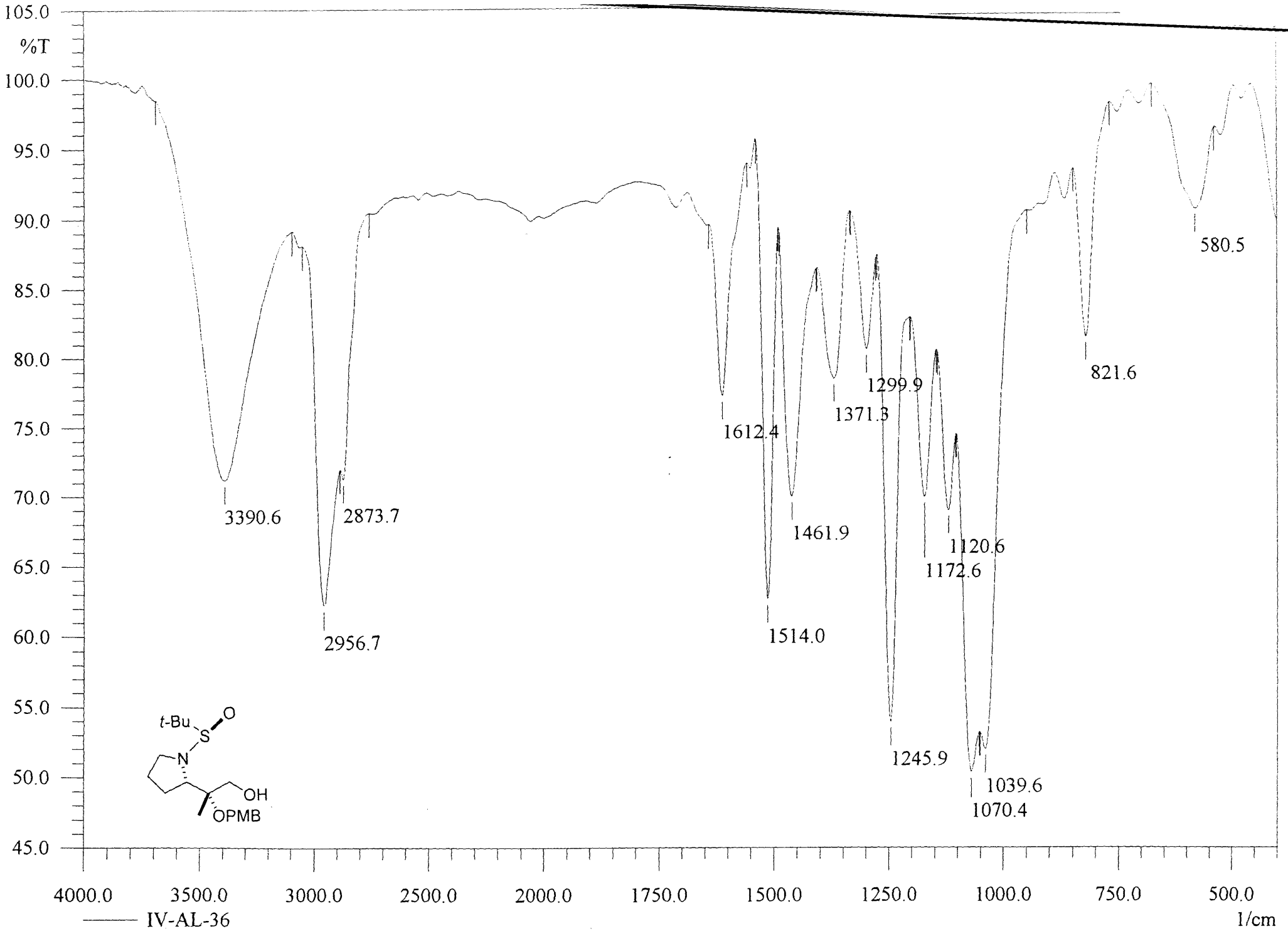




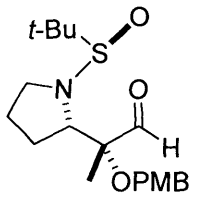
IV-AL-36
HMBC
CDCL3 - 298K



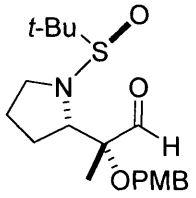

01160806: Scan 424 (84.70 min) - Back
Base: 176.00 Int: 5.75134e+006 Sample: VG 70-SE Positive Ion FAB
Sample: IV-AL-36
Instrument Resolution: 8000
Theoretical Mass: (M+Na) 392.18714
Measured Mass: (M+Na) 392.18674
Error: 1.02 ppm
t-Bu
S
O
N
OH
OPMB
105%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
176
199
214
242
286
323
349
371
392
472
150
200
250
300
350
400
450
500
m/z

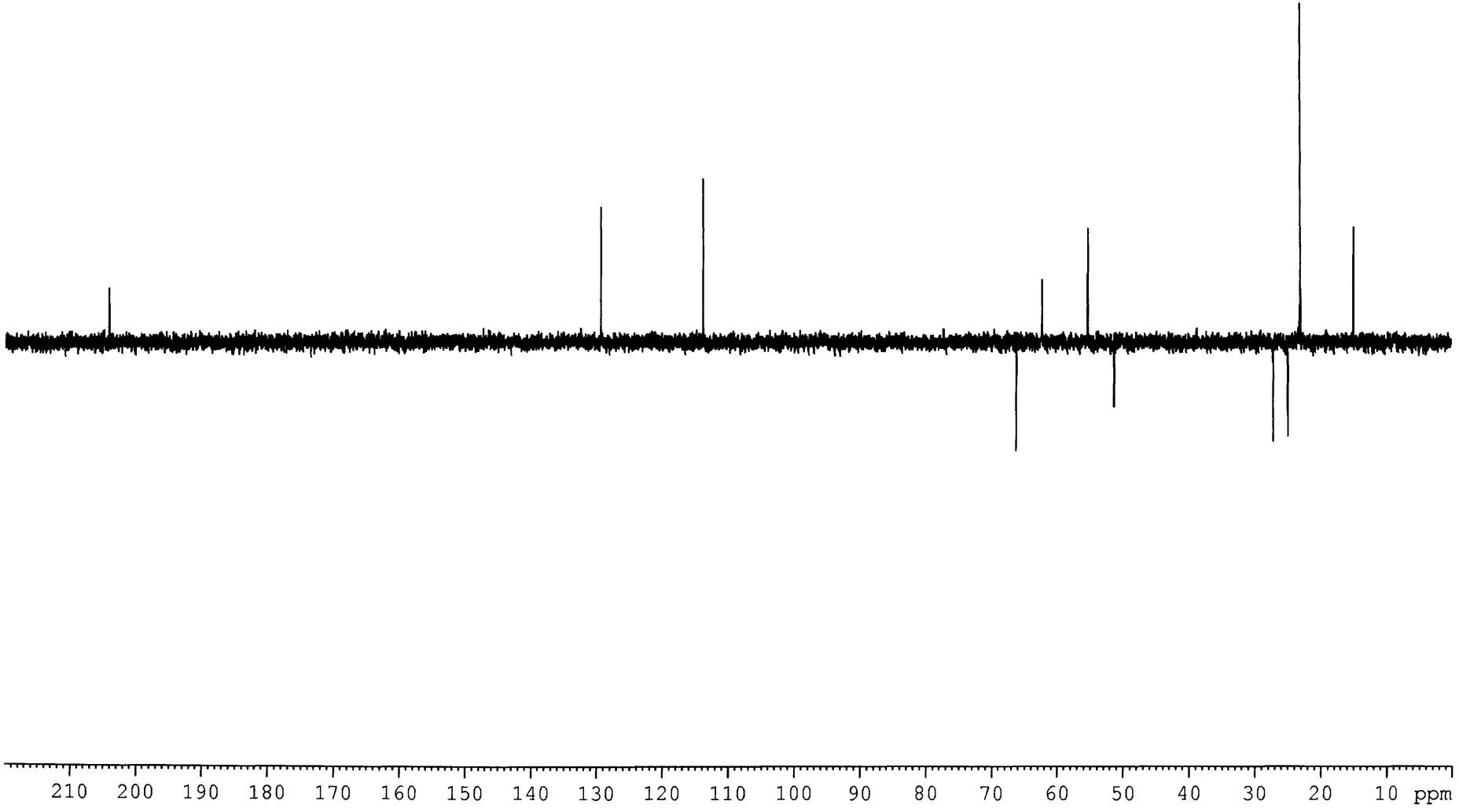

105.0
%T
100.0
95.0
90.0
85.0
80.0
75.0
70.0
65.0
60.0
55.0
50.0
45.0
3390.6
2873.7
2956.7
1612.4
1514.0
1461.9
1371.3
1299.9
1245.9
1172.6
1120.6
1070.4
1039.6
821.6
580.5
t-Bu
S
O
N
OH
OPMB
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
IV-AL-36

IV-AL-38
CDCl3 - 298K

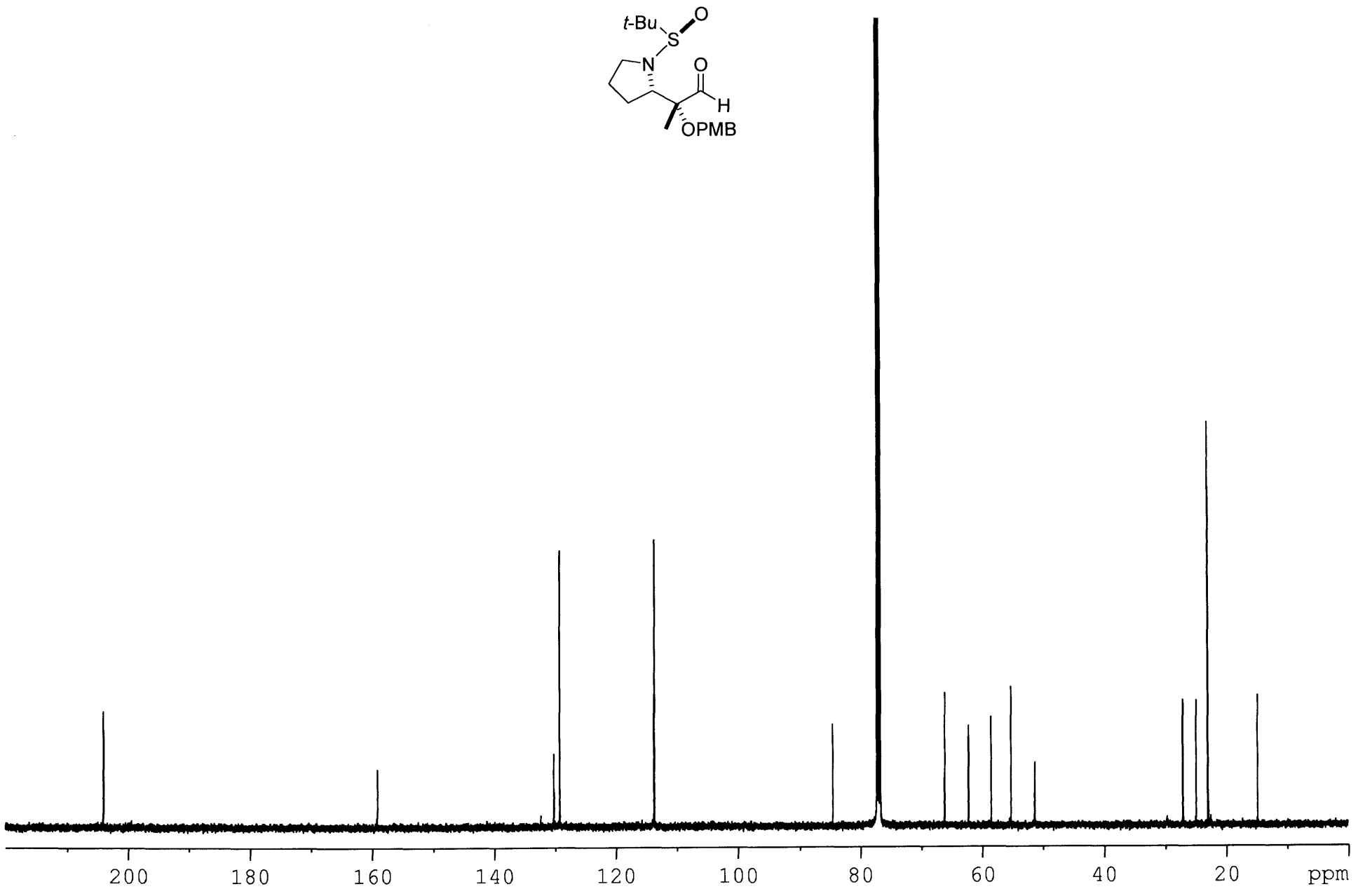


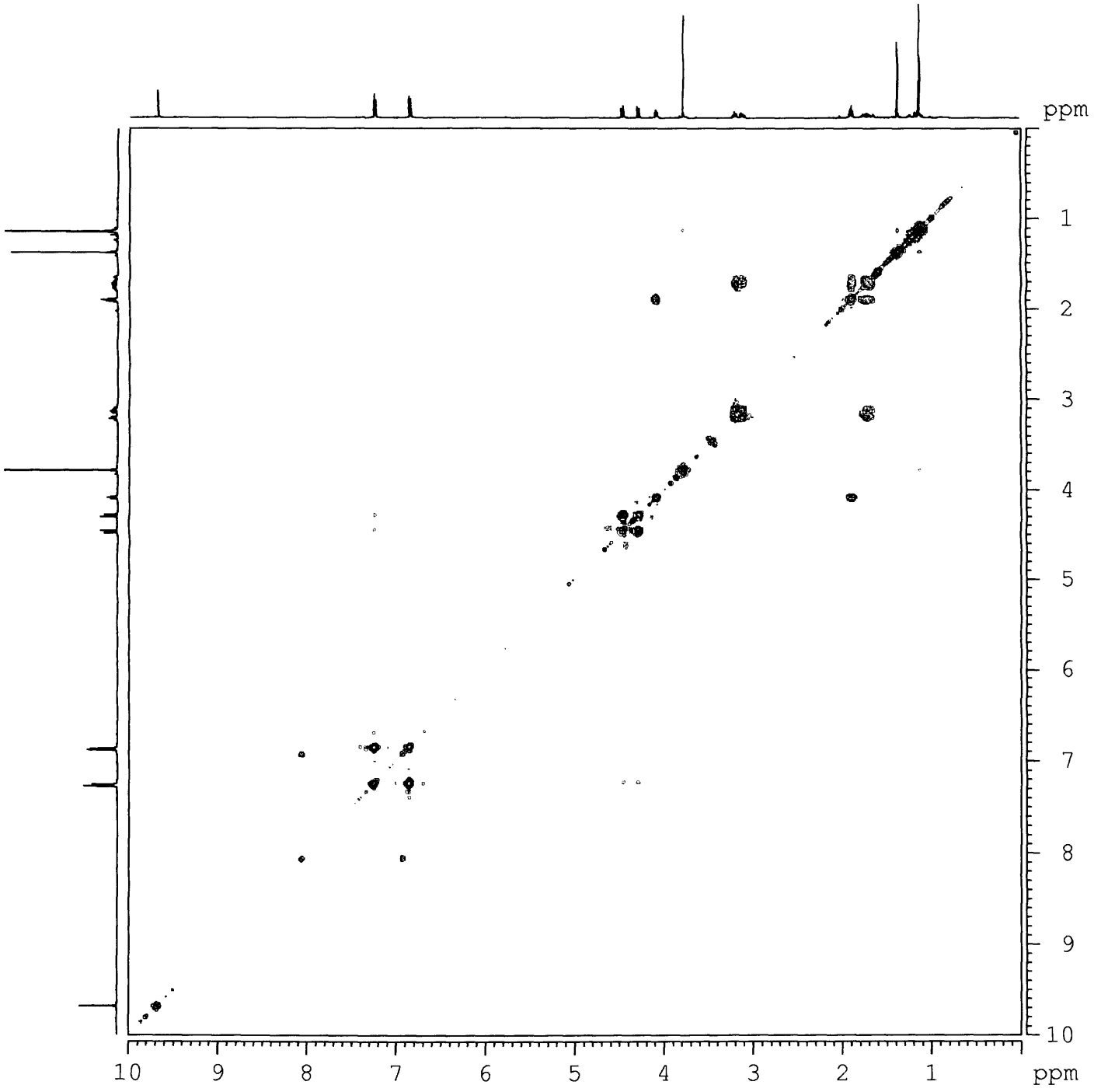
IV-AL-38
DEPT
CDCl3 - 298K



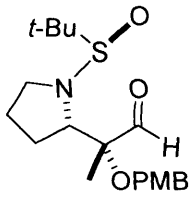


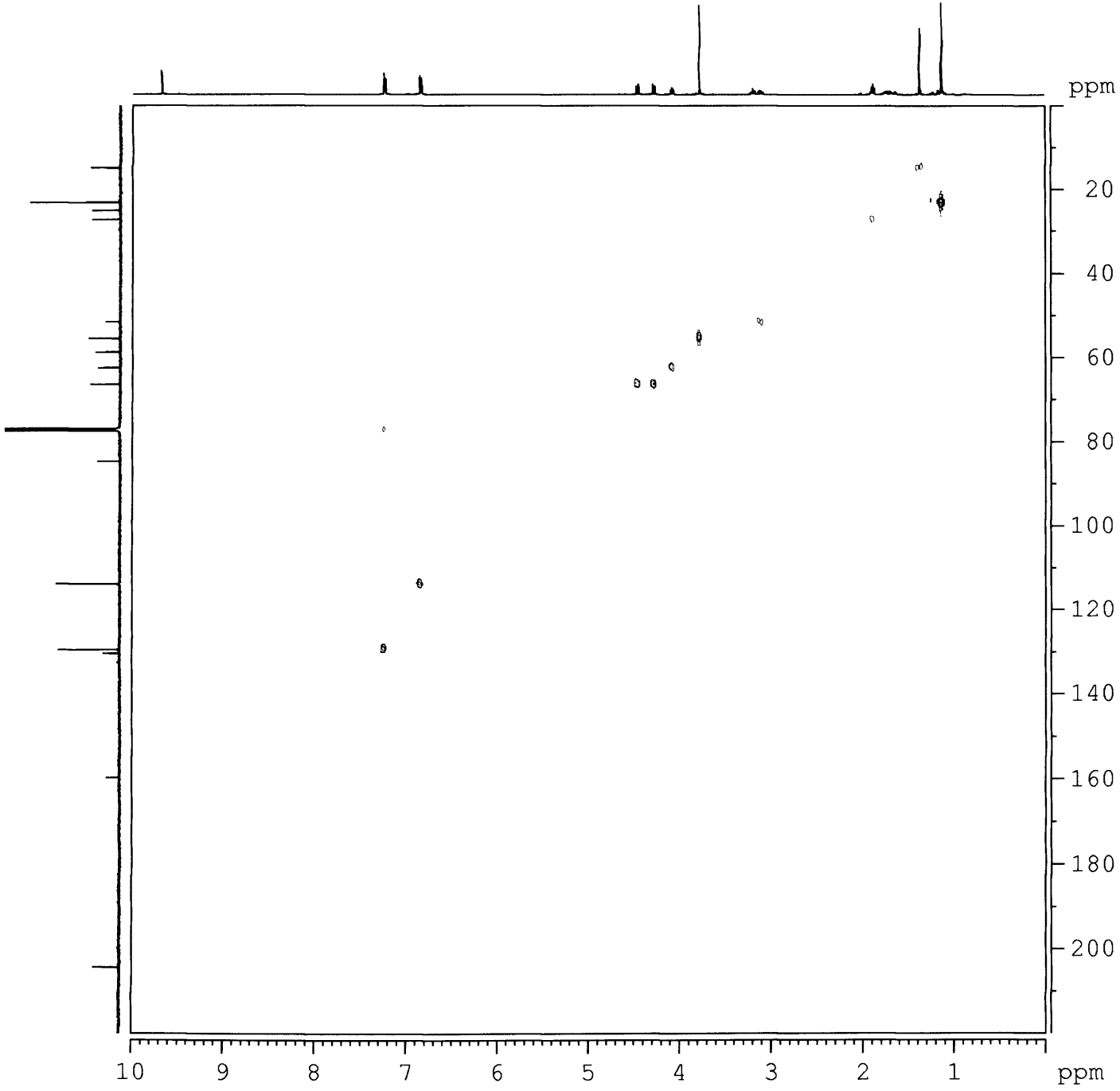
IV-AL-38
13C
CDCl3 - 298K



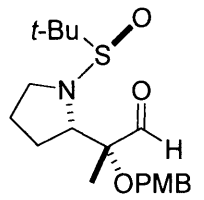


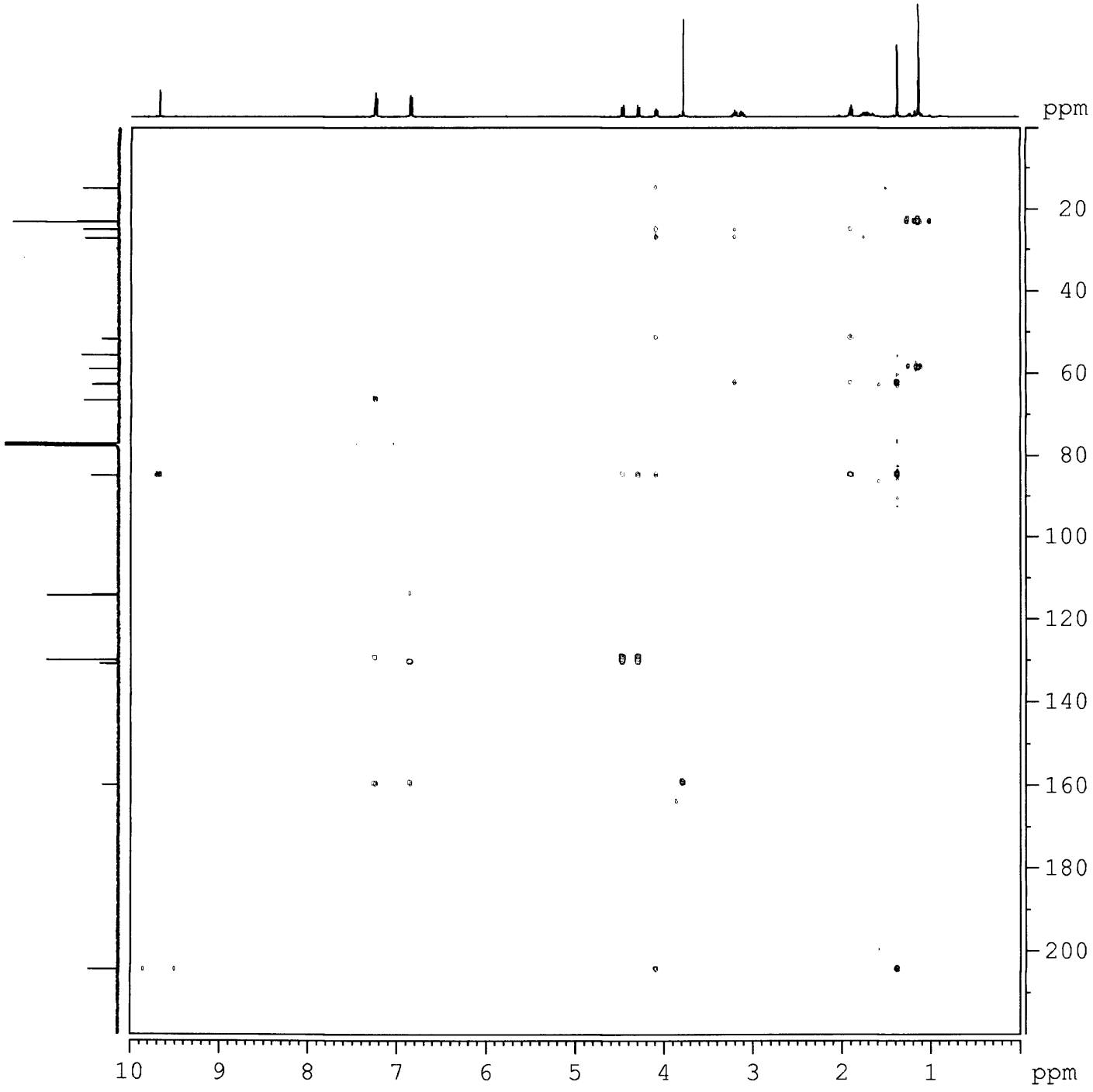
IV-AL-38
cosy
CDCl3 - 298K



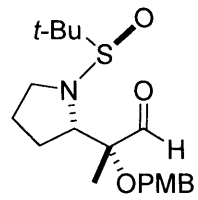


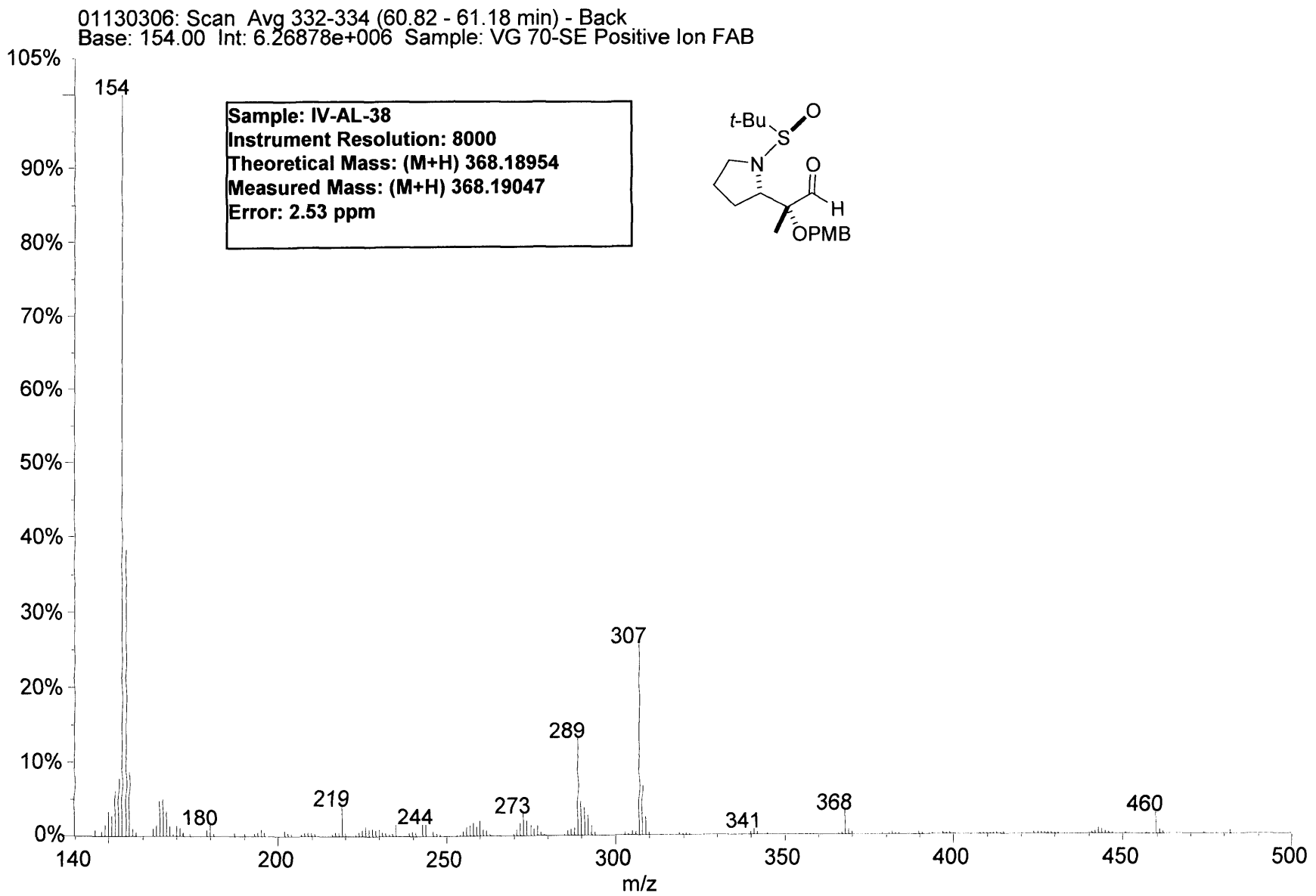
IV-AL-38
HMQC
CDCl3 - 298K

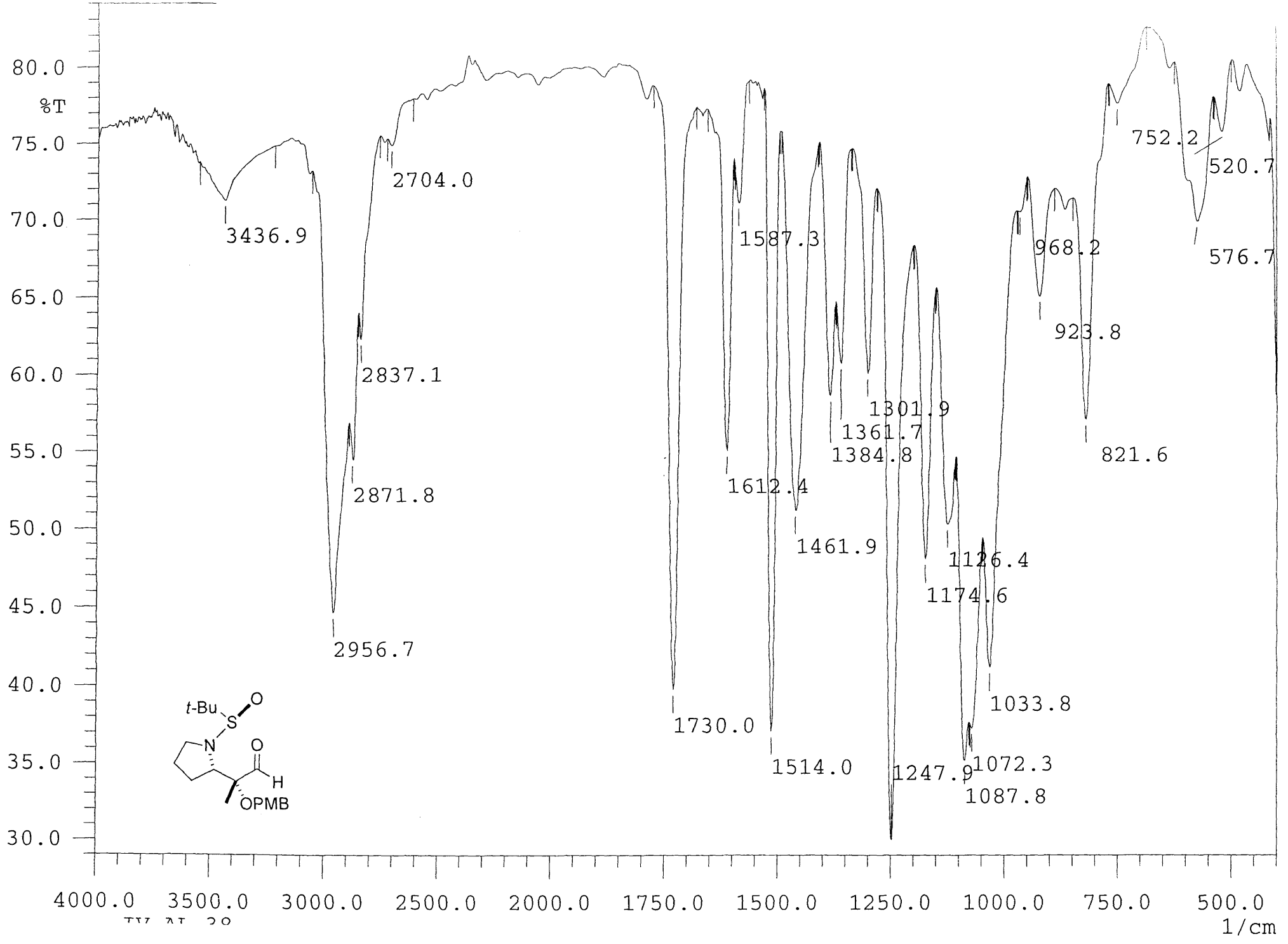




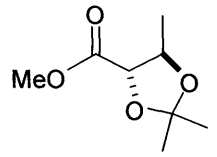
IV-AL-38
HMBC
CDCl3 - 298K



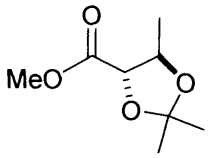

01130306: Scan Avg 332-334 (60.82 - 61.18 min) - Back
Base: 154.00 Int: 6.26878e+006 Sample: VG 70-SE Positive Ion FAB
Sample: IV-AL-38
Instrument Resolution: 8000
Theoretical Mass: (M+H) 368.18954
Measured Mass: (M+H) 368.19047
Error: 2.53 ppm
t-Bu
S
O
N
O
H
OPMB
105%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
154
180
219
244
273
289
307
341
368
460
140
200
250
300
350
400
450
500
m/z

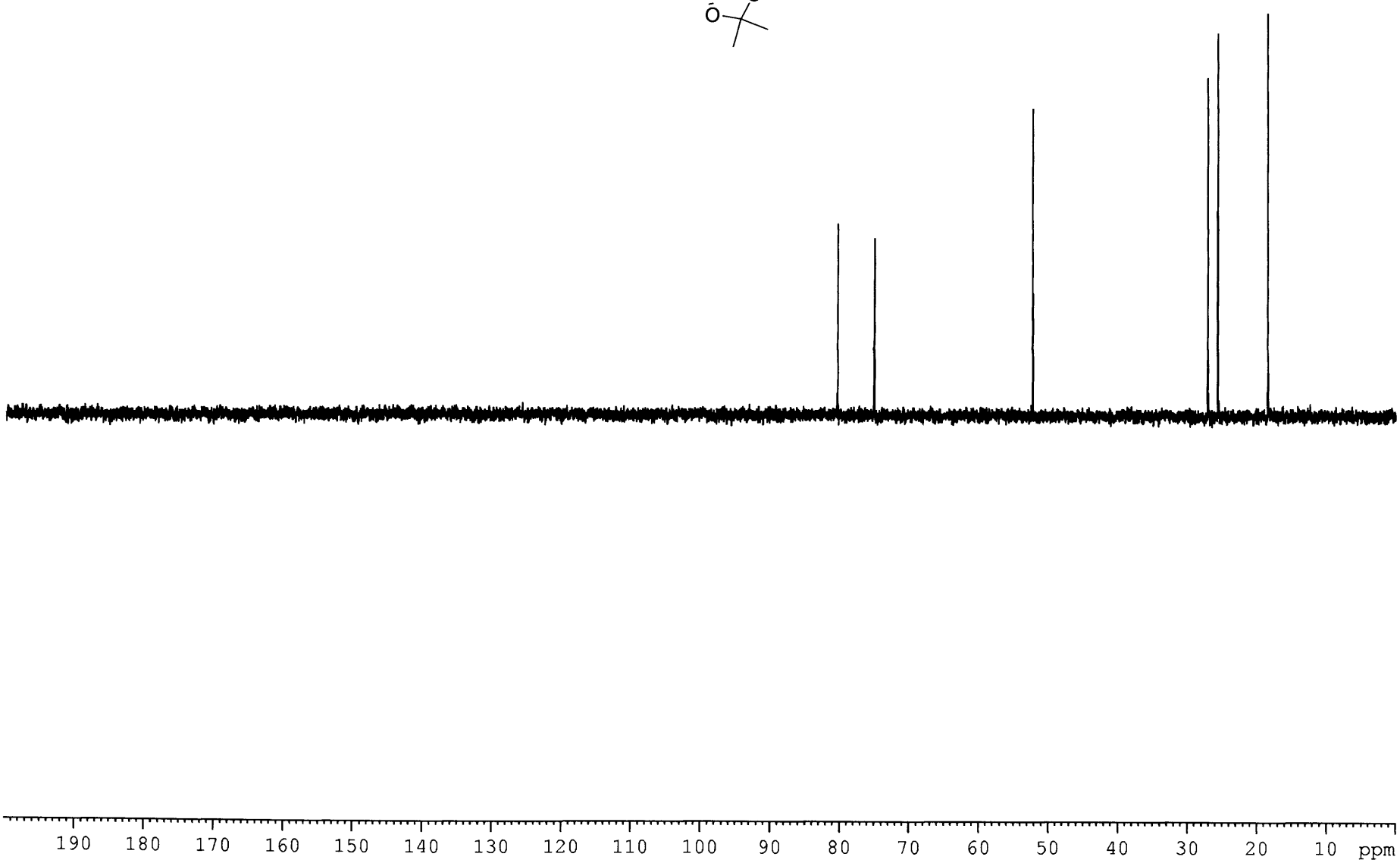

80.0
%T
75.0
70.0
65.0
60.0
55.0
50.0
45.0
40.0
35.0
30.0
3436.9
2704.0
2837.1
2871.8
2956.7
1730.0
1587.3
1612.4
1514.0
1461.9
1301.9
1361.7
1384.8
1247.9
1174.6
1126.4
1087.8
1072.3
1033.8
968.2
923.8
821.6
752.2
520.7
576.7
t-Bu
S
O
N
O
H
OPMB
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm

IV-AL-138
CDCl3 - 298K

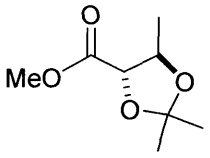


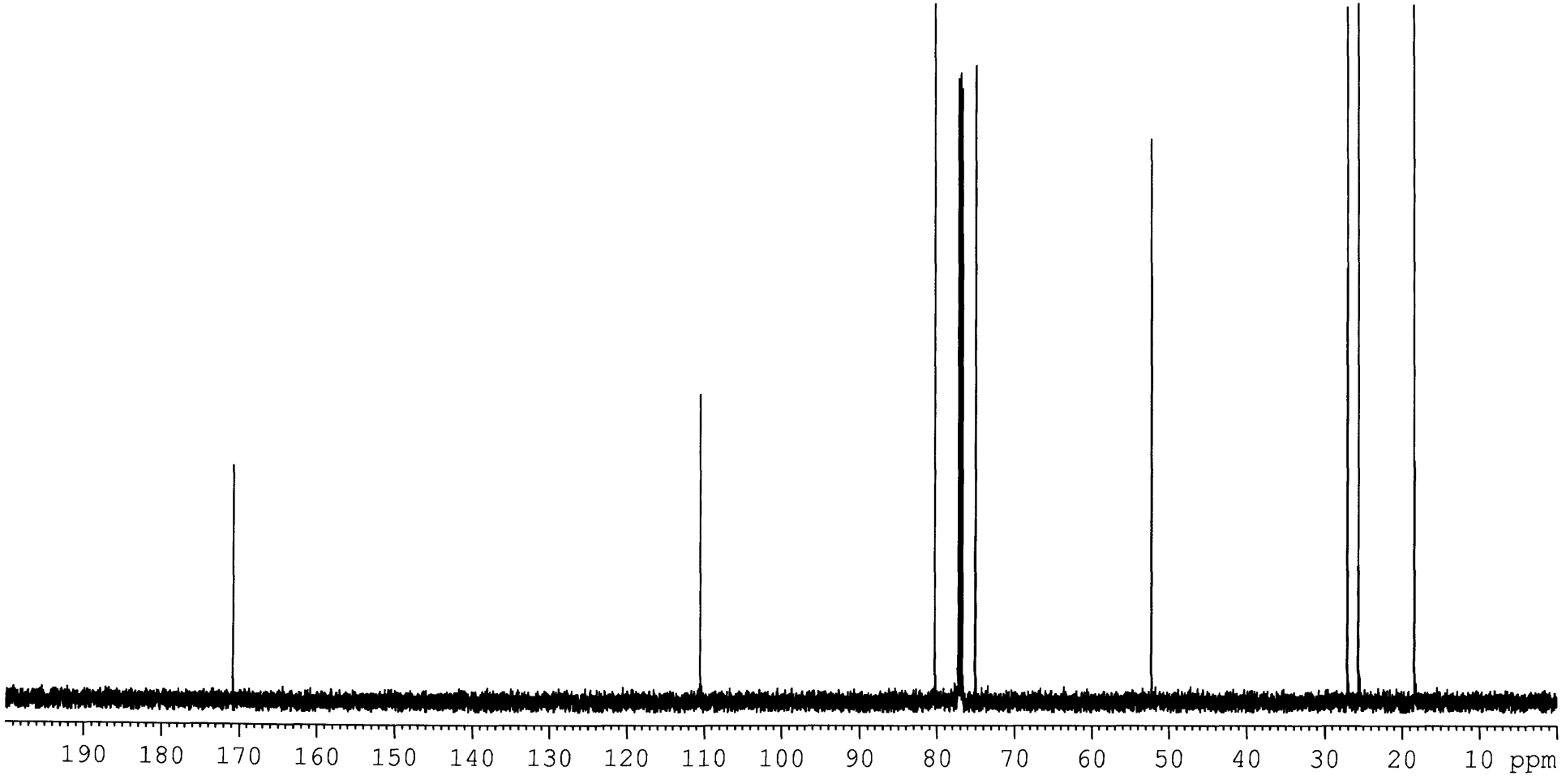
IV-AL-138
DEPT
CDCl3 - 298K



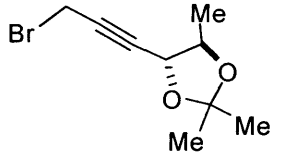


IV-AL-138
13C
CDCl3 - 298K

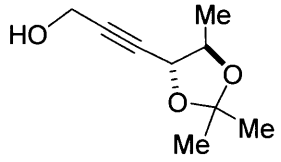




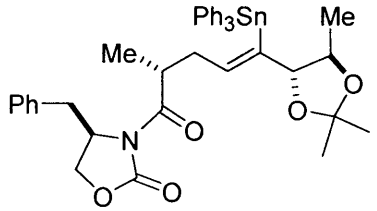
IV-AL-111
CDCl3 - 298K

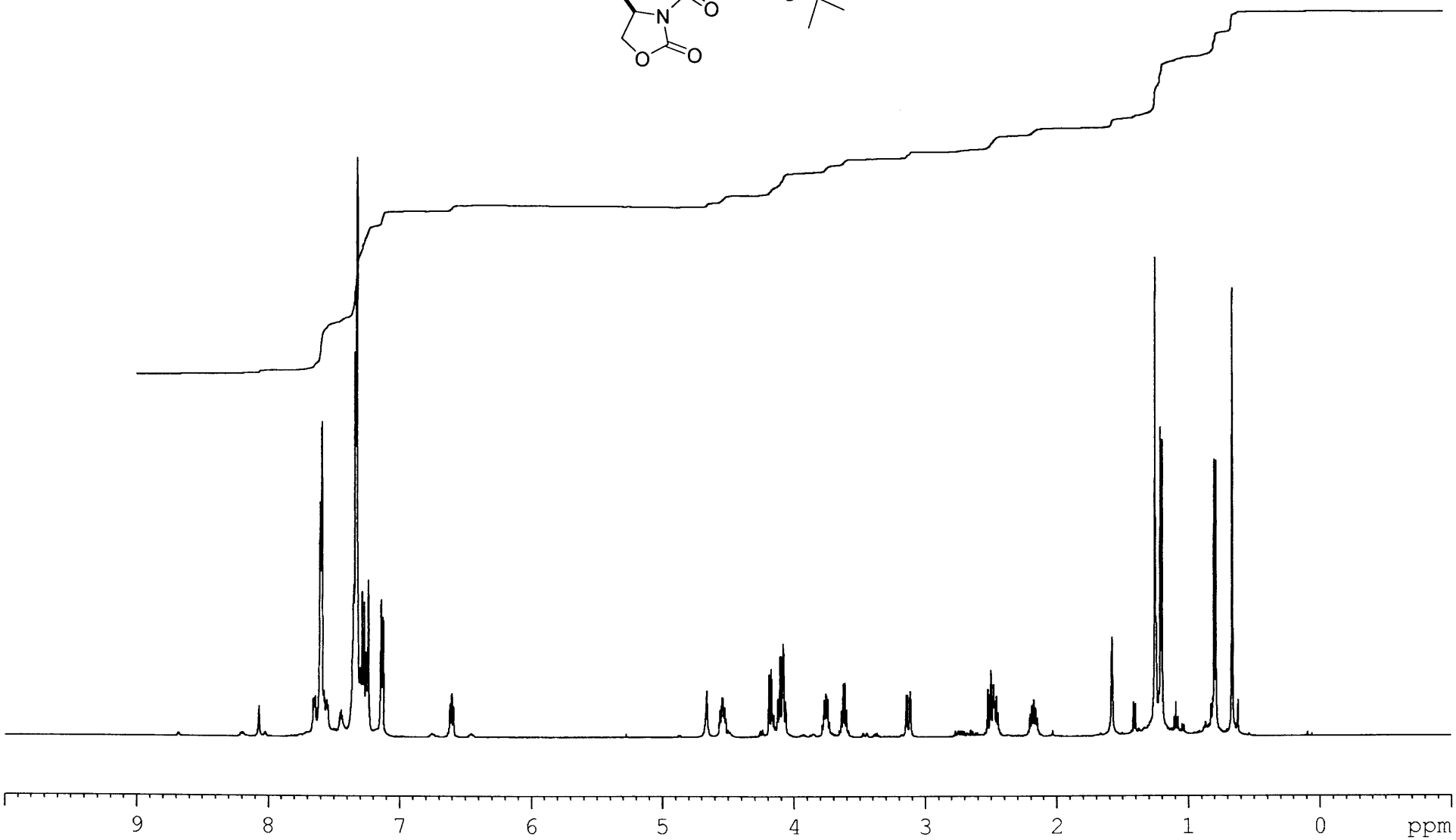


IV-AL-62
CDCl3 - 298K

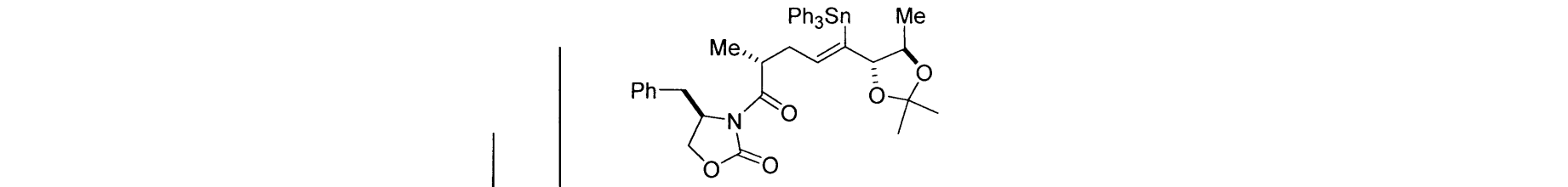


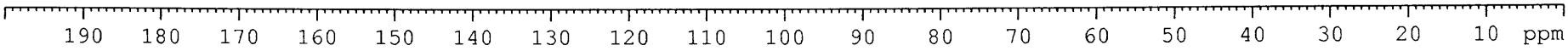
IV-AL-122
CDCl3 - 298K



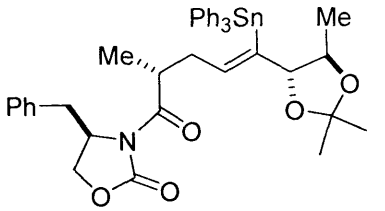


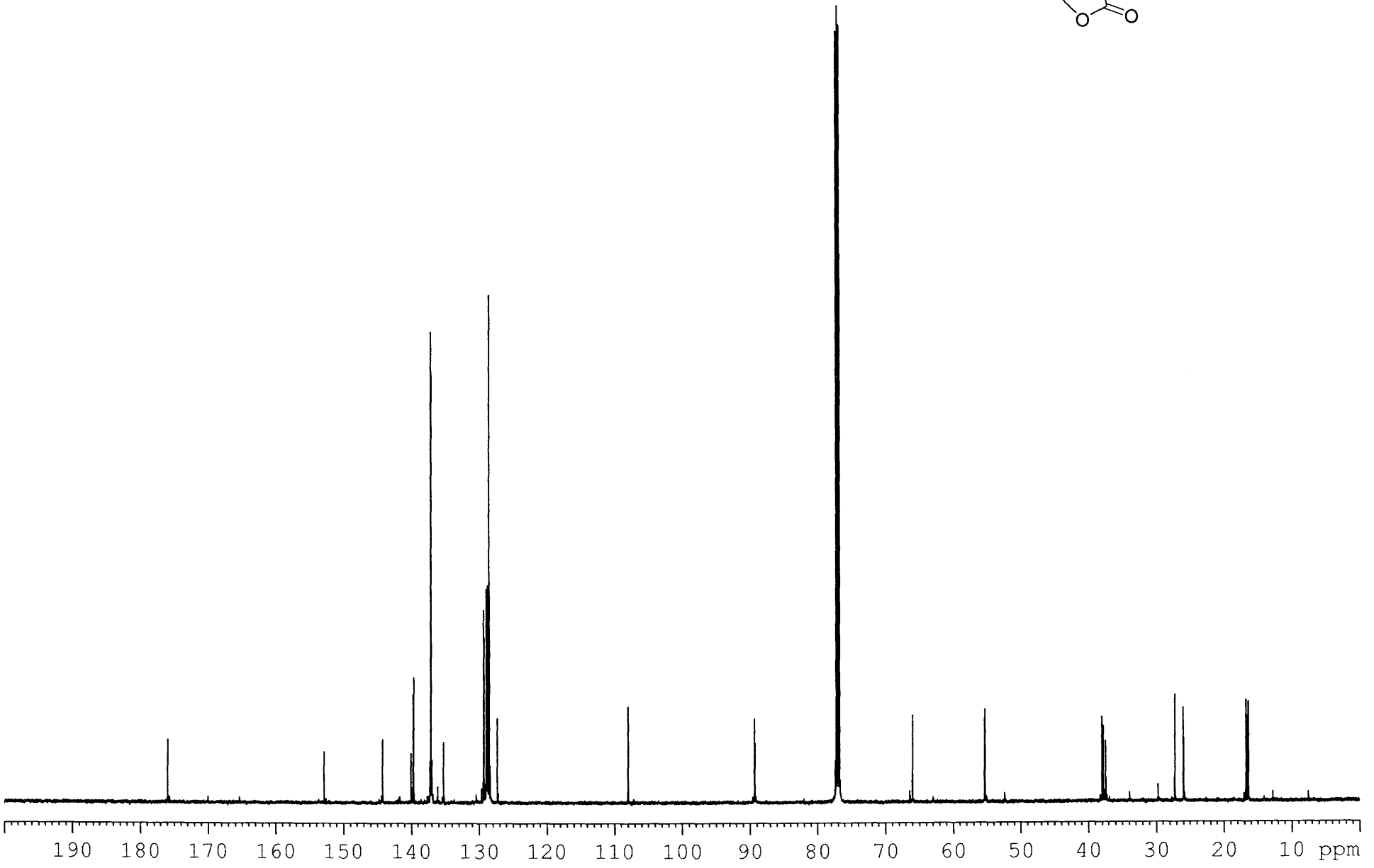
IV-AL-122
DEPT
CDCl3 - 298K

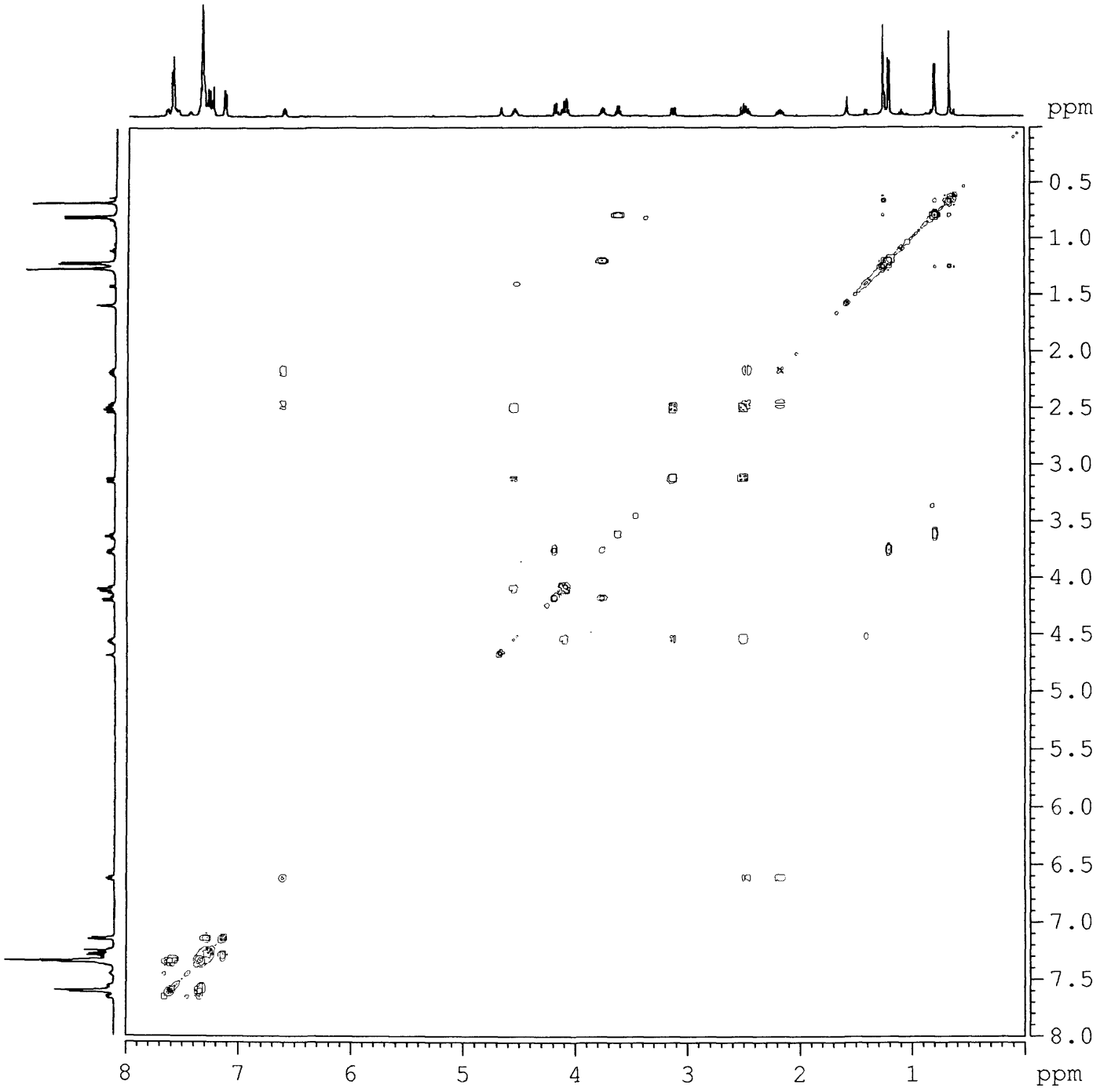




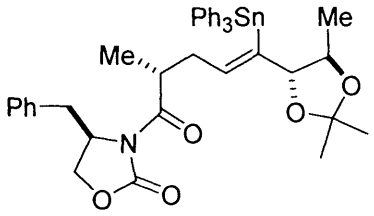
IV-AL-122
13C
CDCl3 - 298K

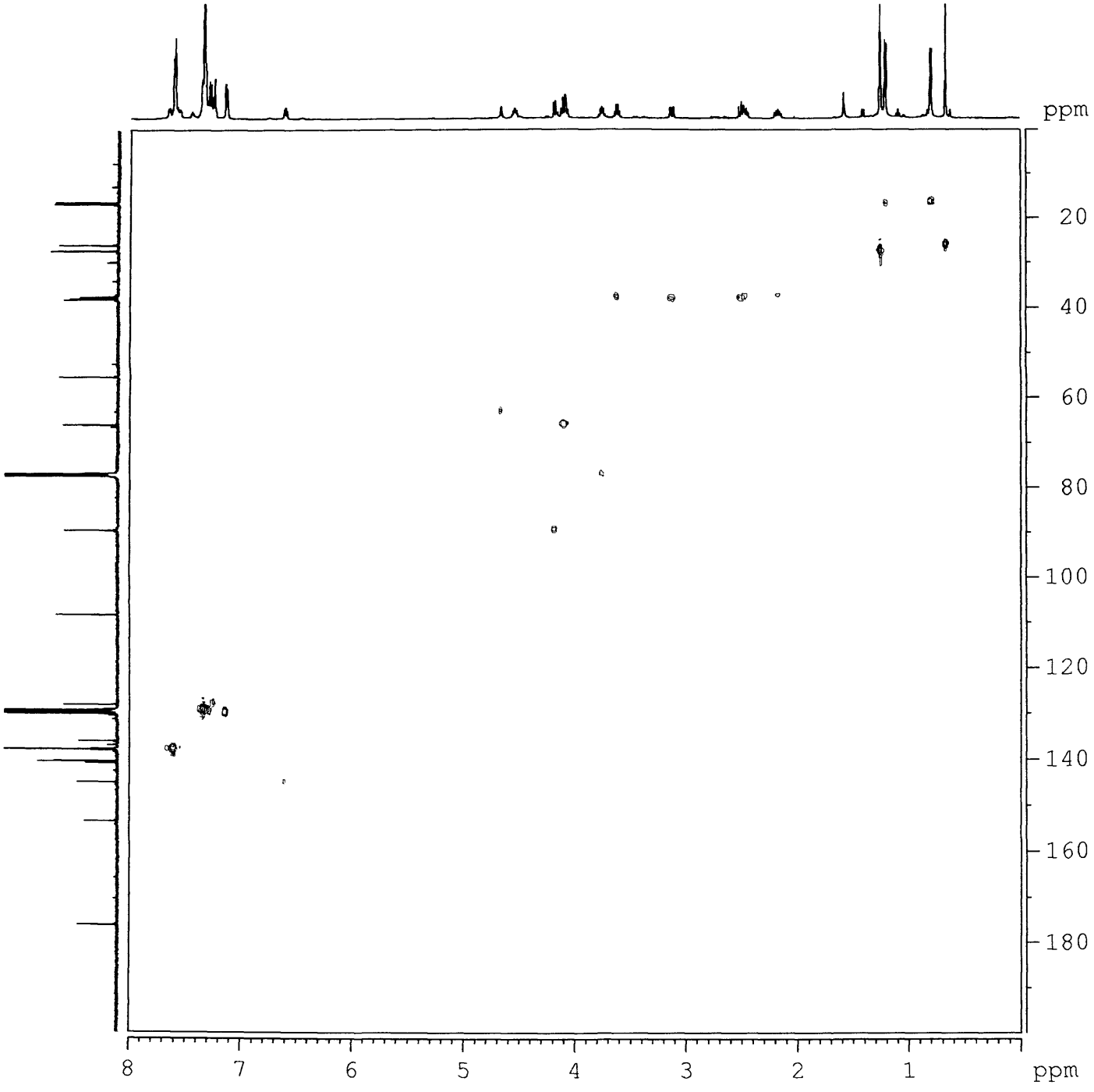




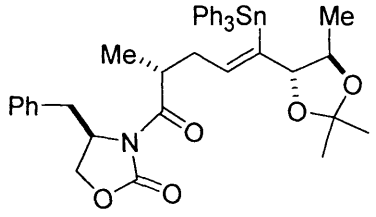


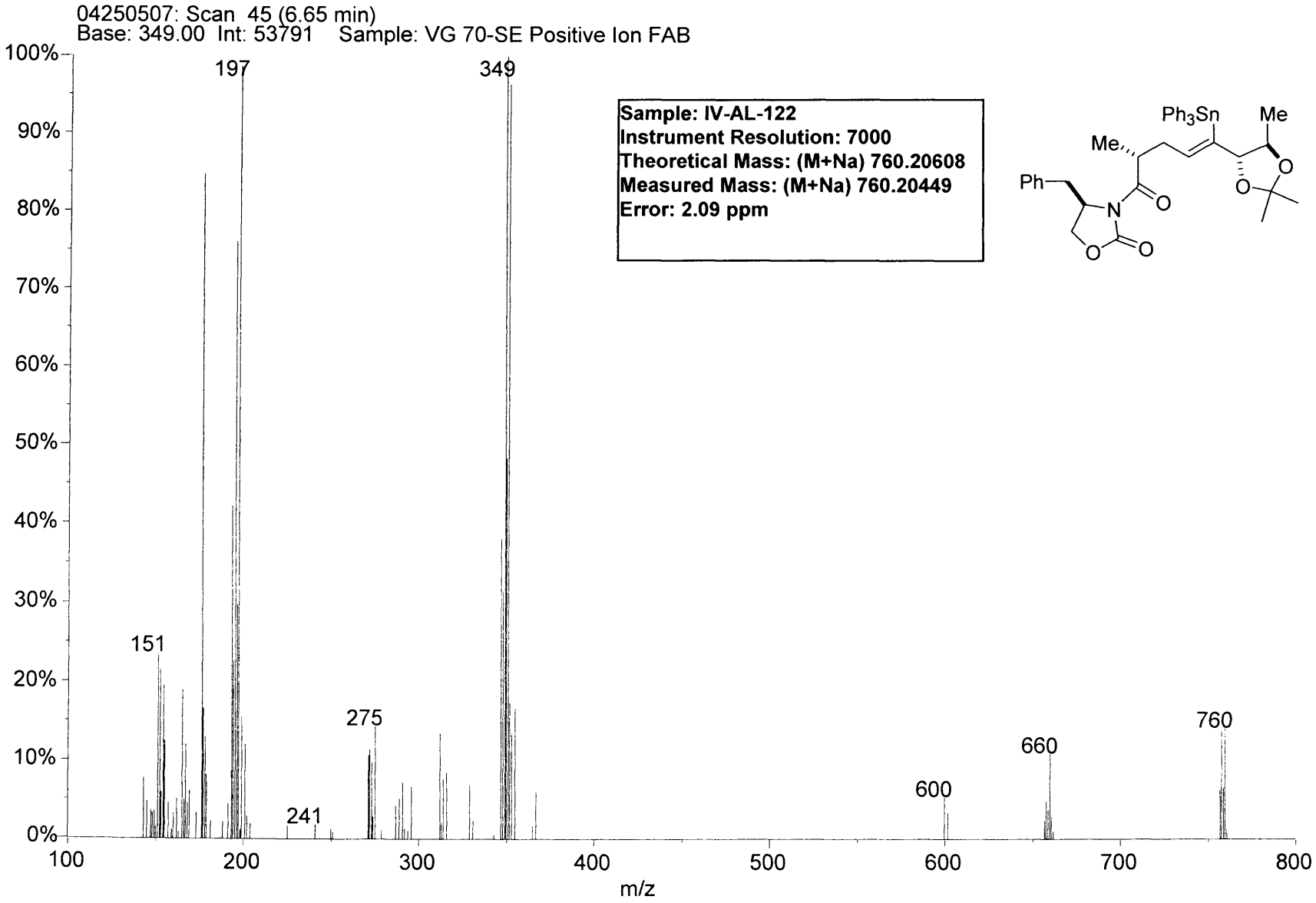
IV-AL-122
COSY
CDCl3 - 298K

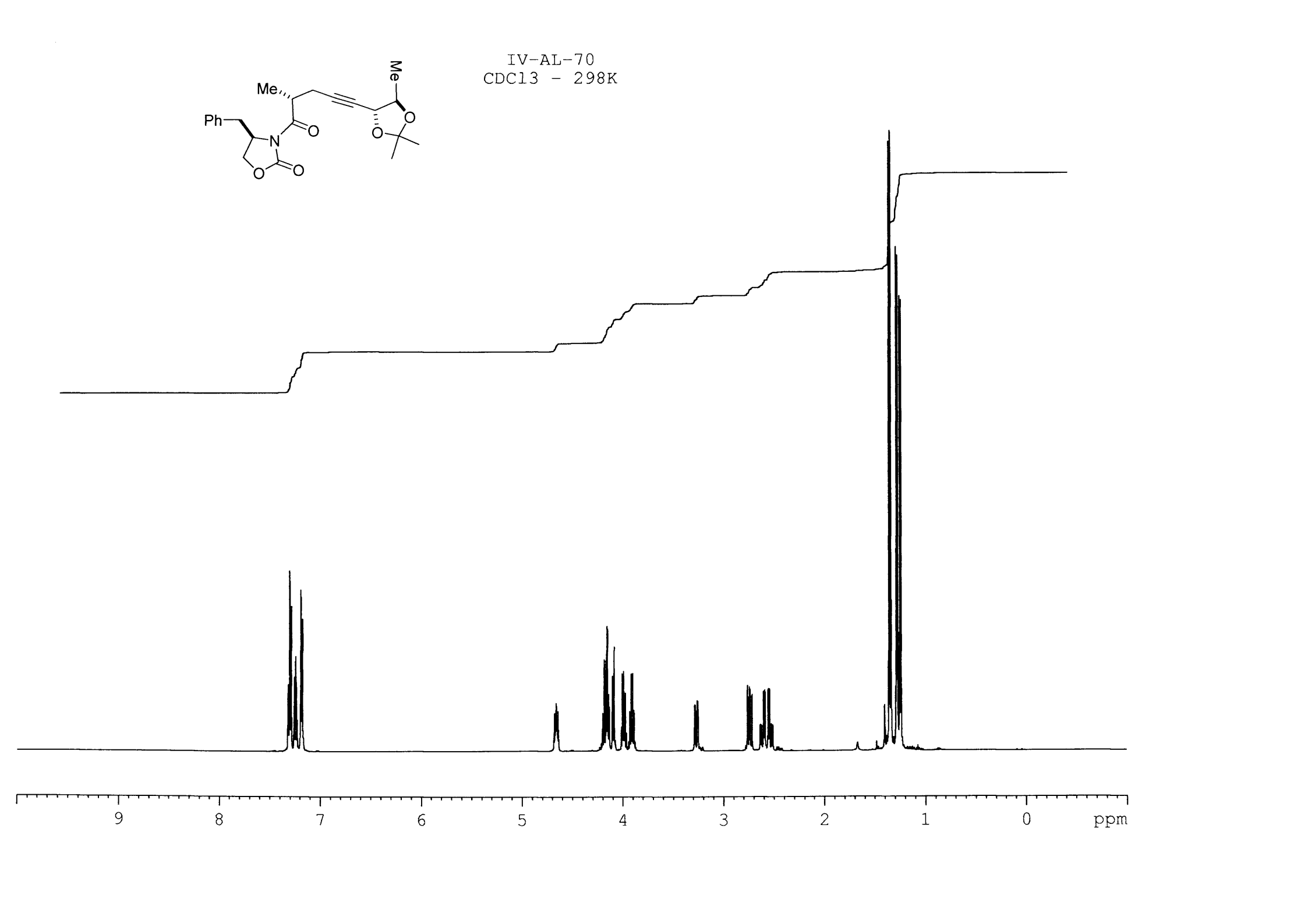




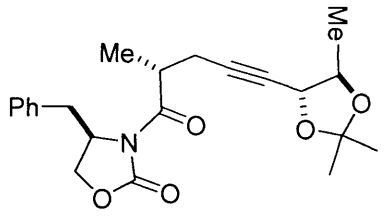
IV-AL-122
HMQC
CDCl3 - 298K

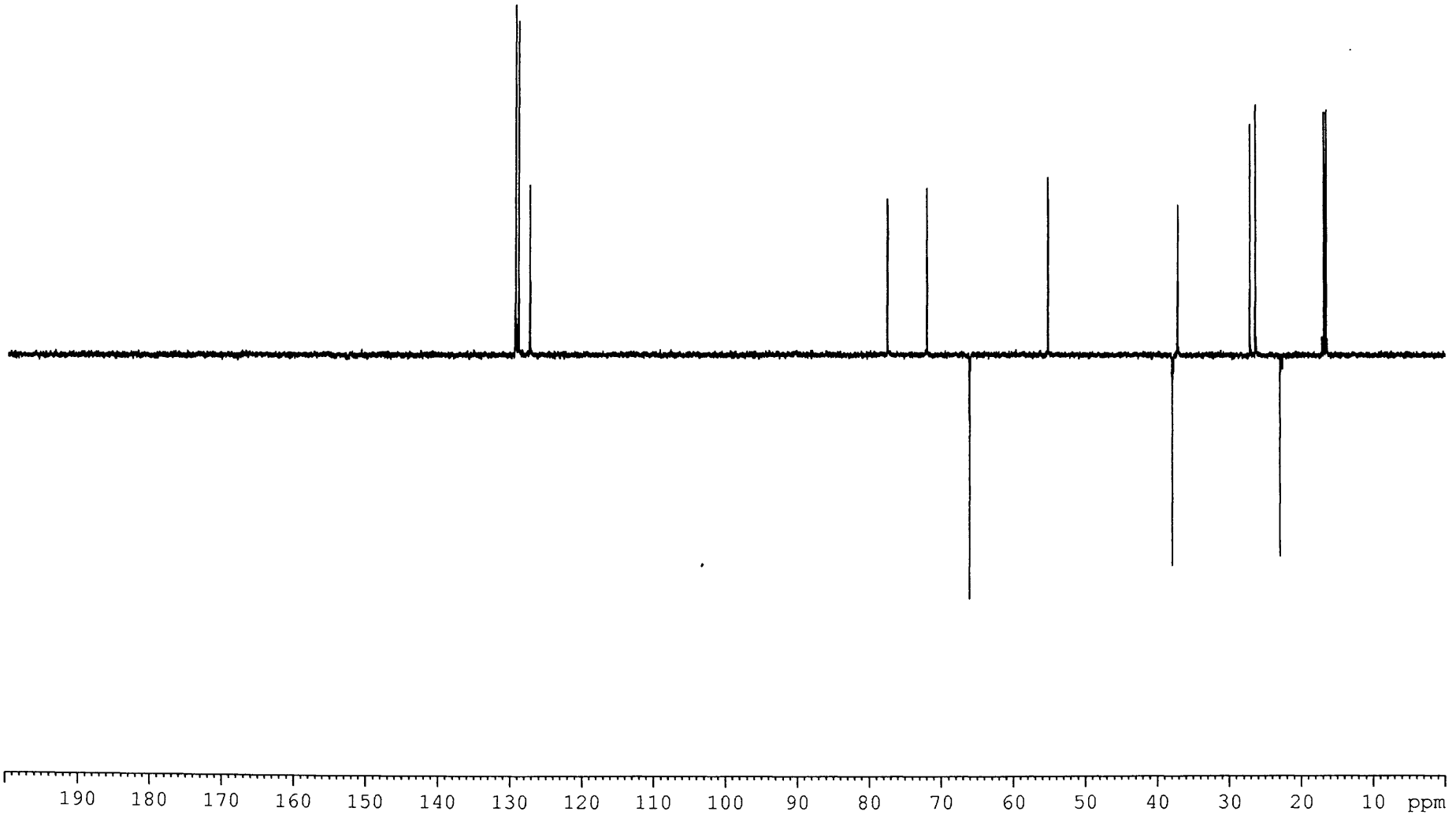



04250507: Scan 45 (6.65 min)
Base: 349.00 Int: 53791 Sample: VG 70-SE Positive Ion FAB
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
197
349
151
275
241
600
660
760
100
200
300
400
500
600
700
800
m/z
Sample: IV-AL-122
Instrument Resolution: 7000
Theoretical Mass: (M+Na) 760.20608
Measured Mass: (M+Na) 760.20449
Error: 2.09 ppm
Ph3Sn
Me
Me
Ph
N
O
O
O
O
O
O

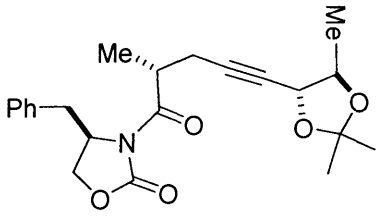

IV-AL-70
CDCl3 - 298K
Me
Me
Ph
N
O
O
O
O
O
9
8
7
6
5
4
3
2
1
0
ppm

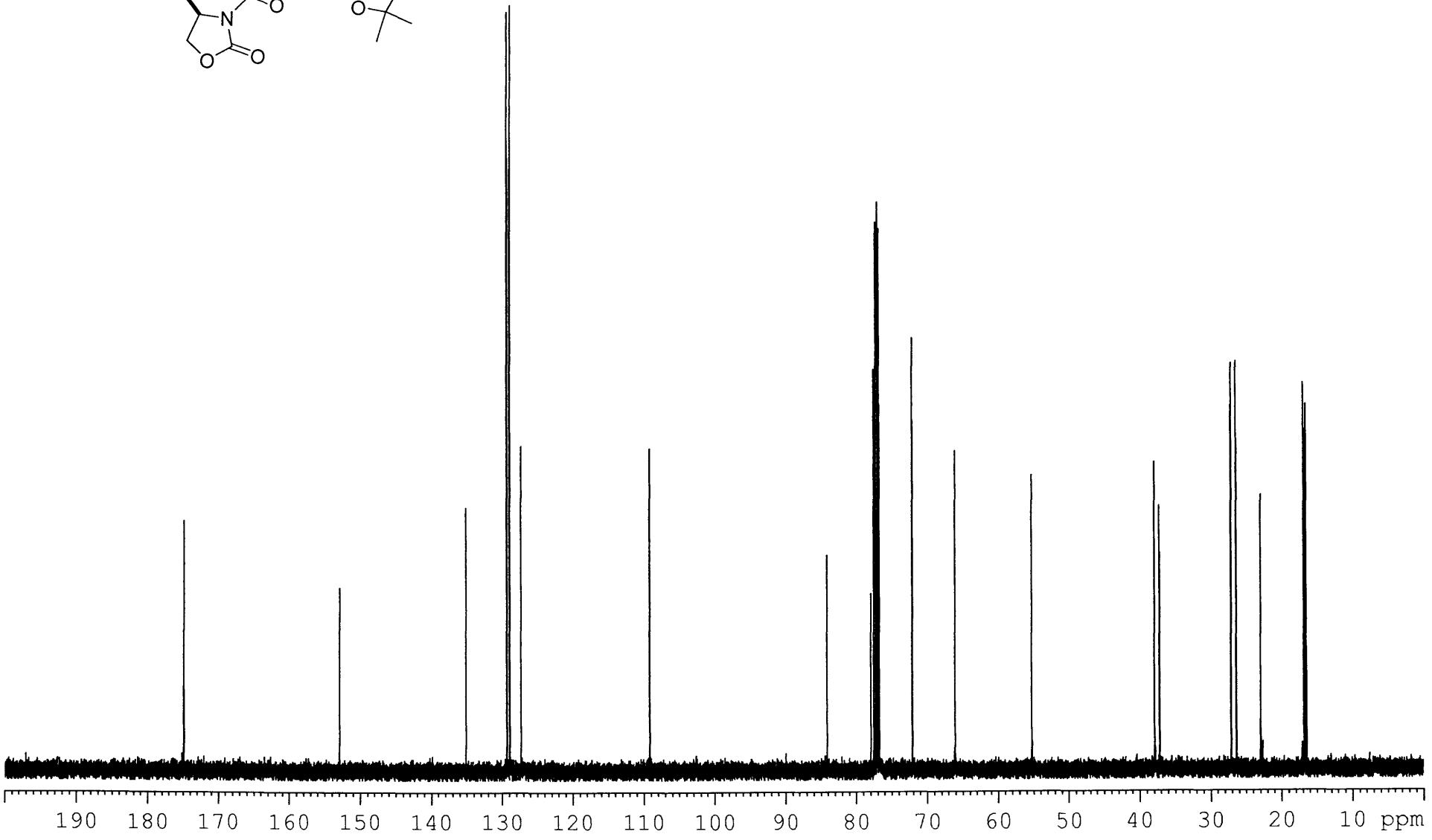
IV-AL-70
DEPT
CDCl3 - 298K

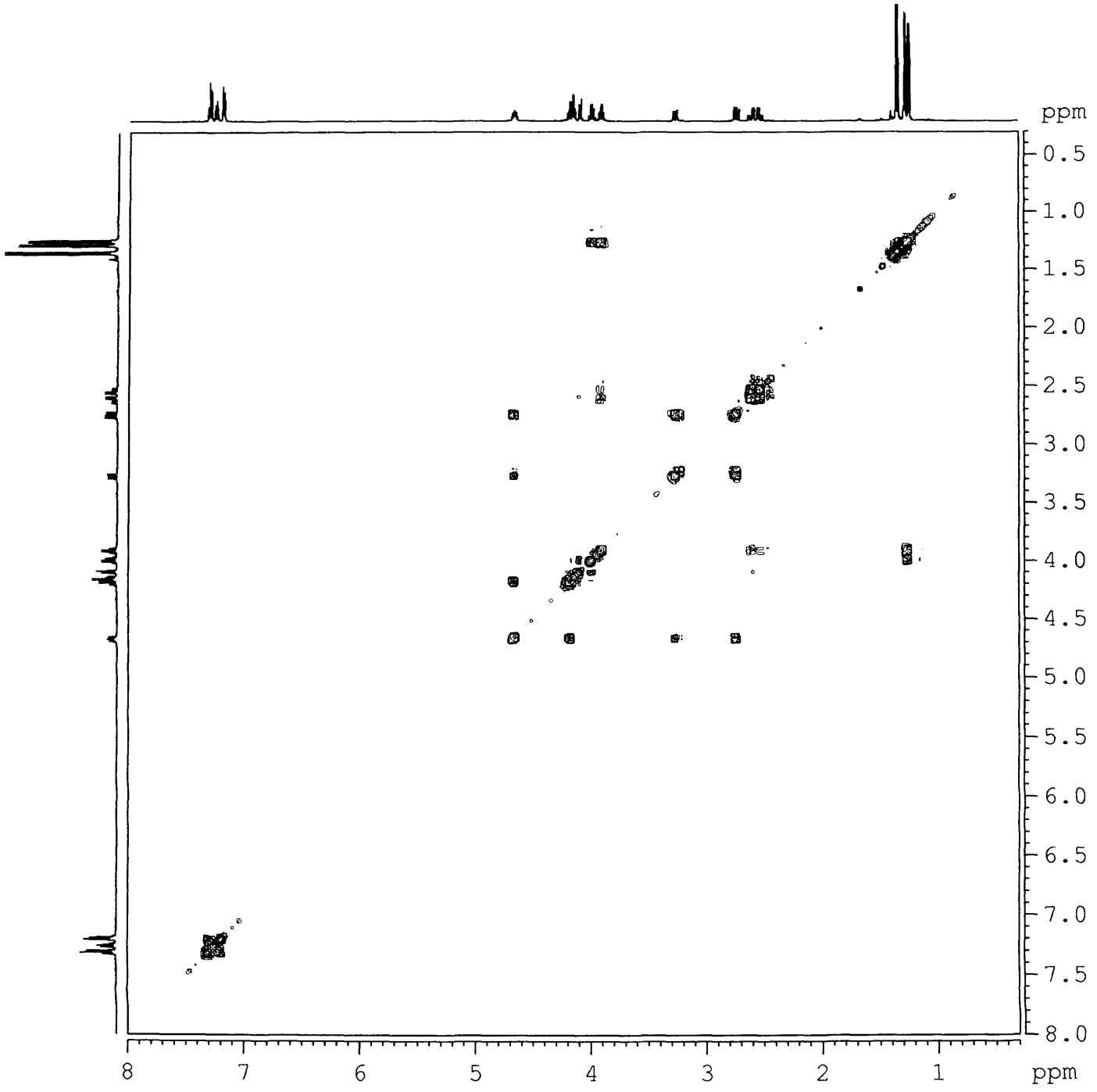




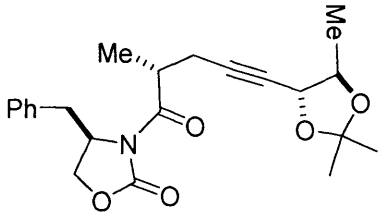
IV-AL-70
13C
CDCl3 - 298K

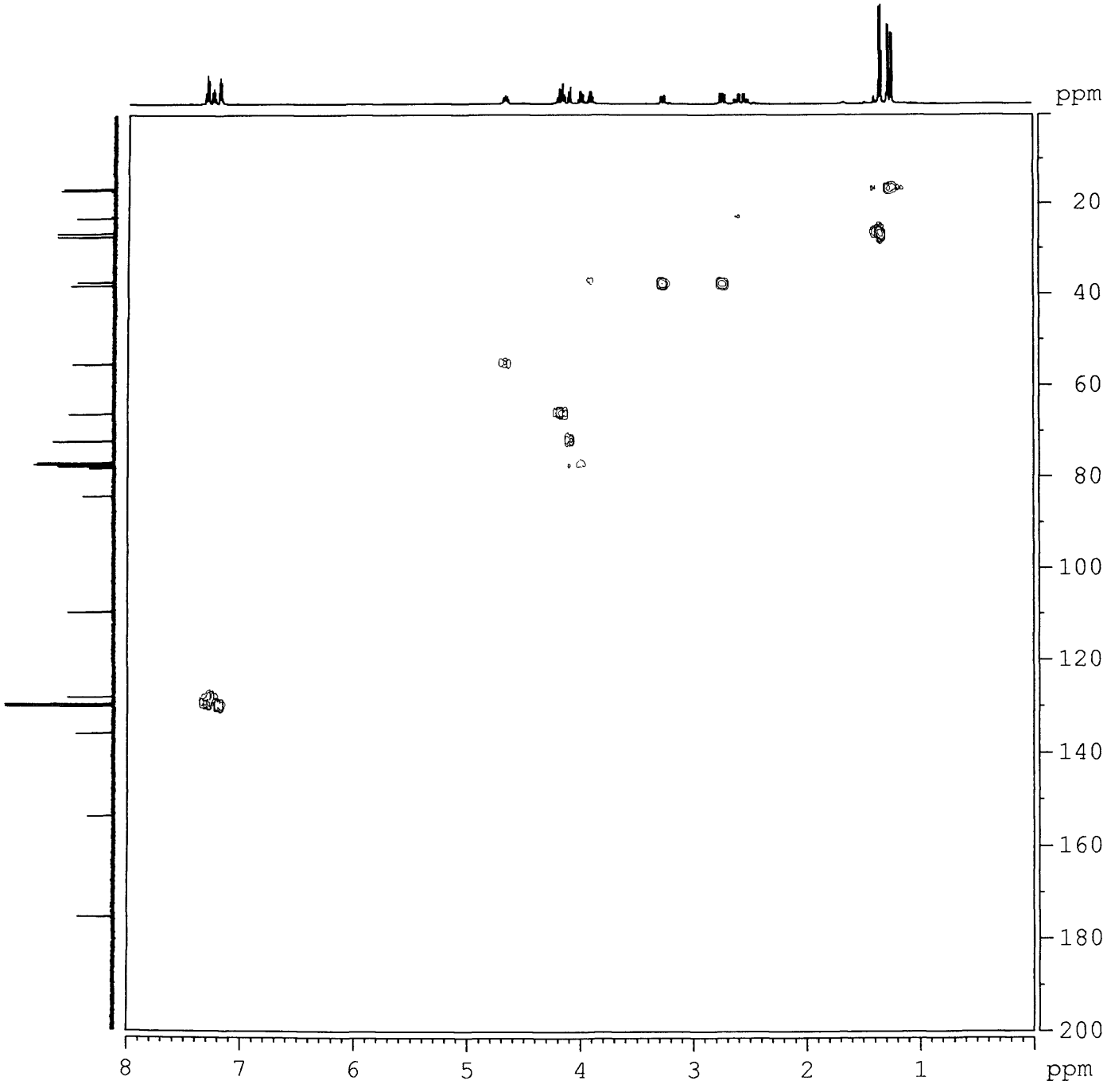




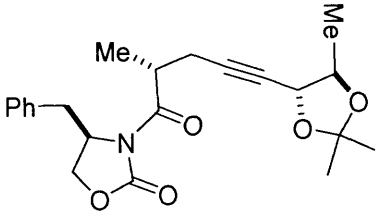


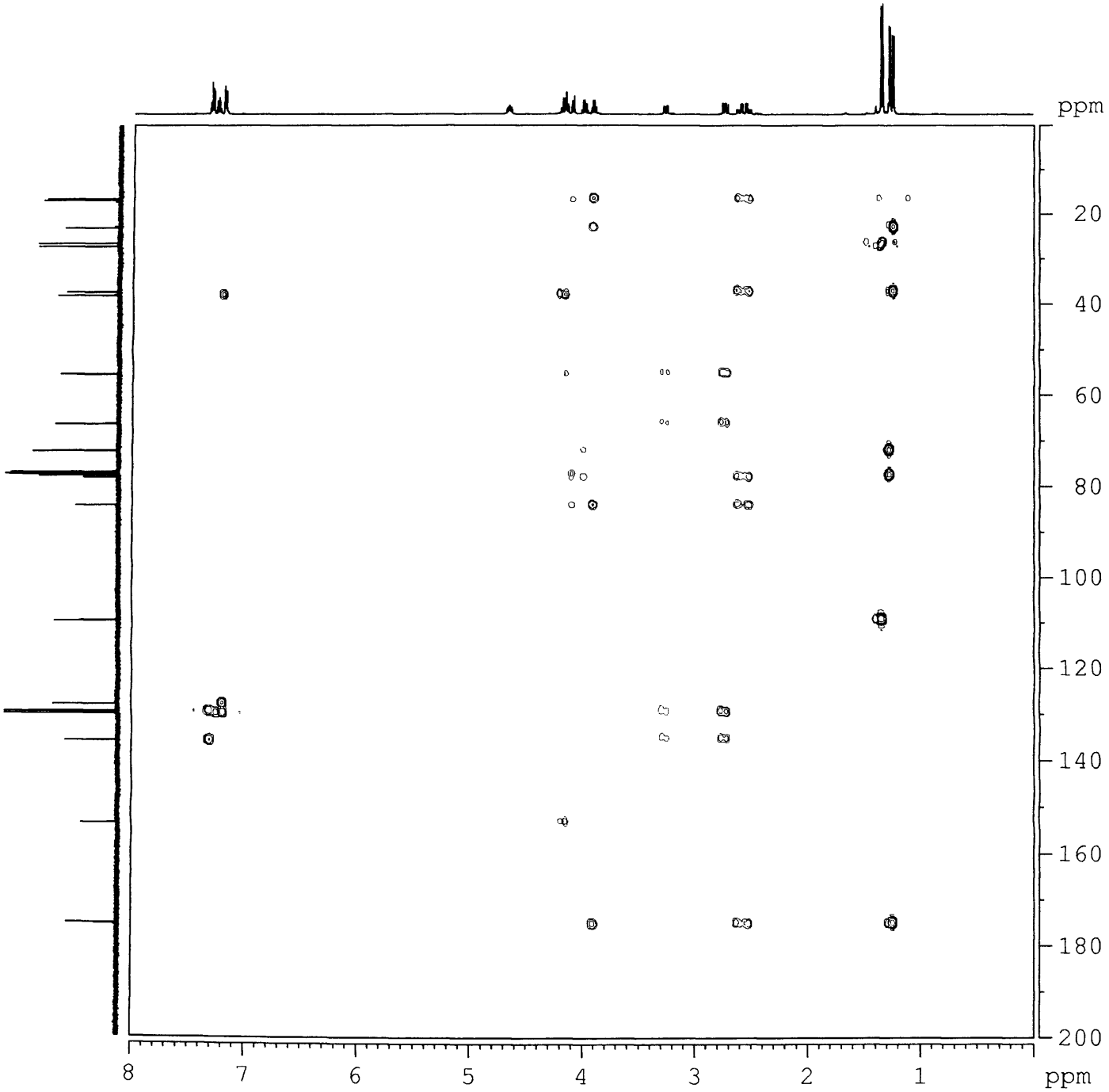
IV-AL-70
COSY
CDCl3 - 298K



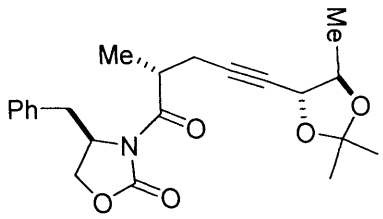


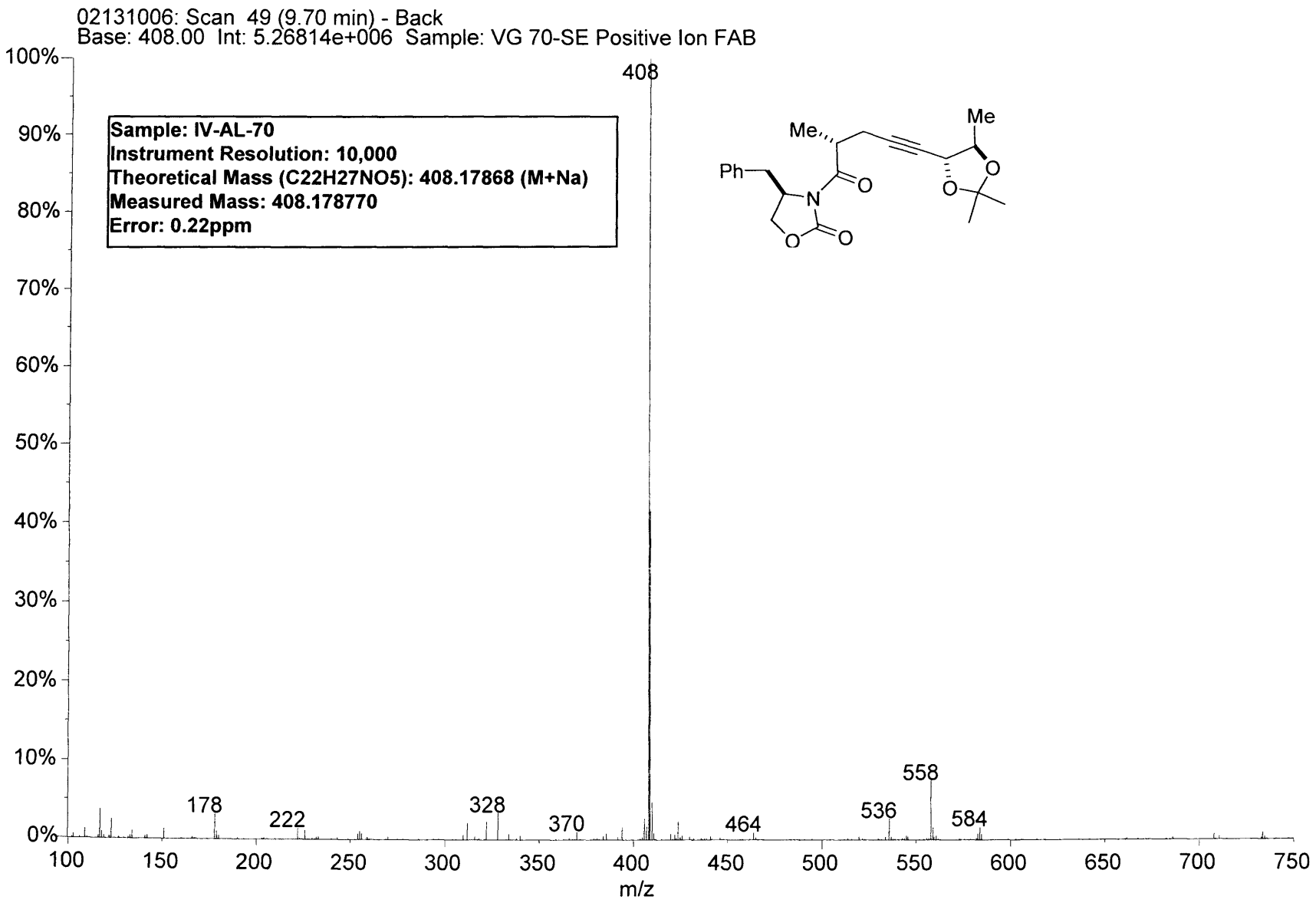
IV-AL-70
HMQC
CDCl3 - 298K

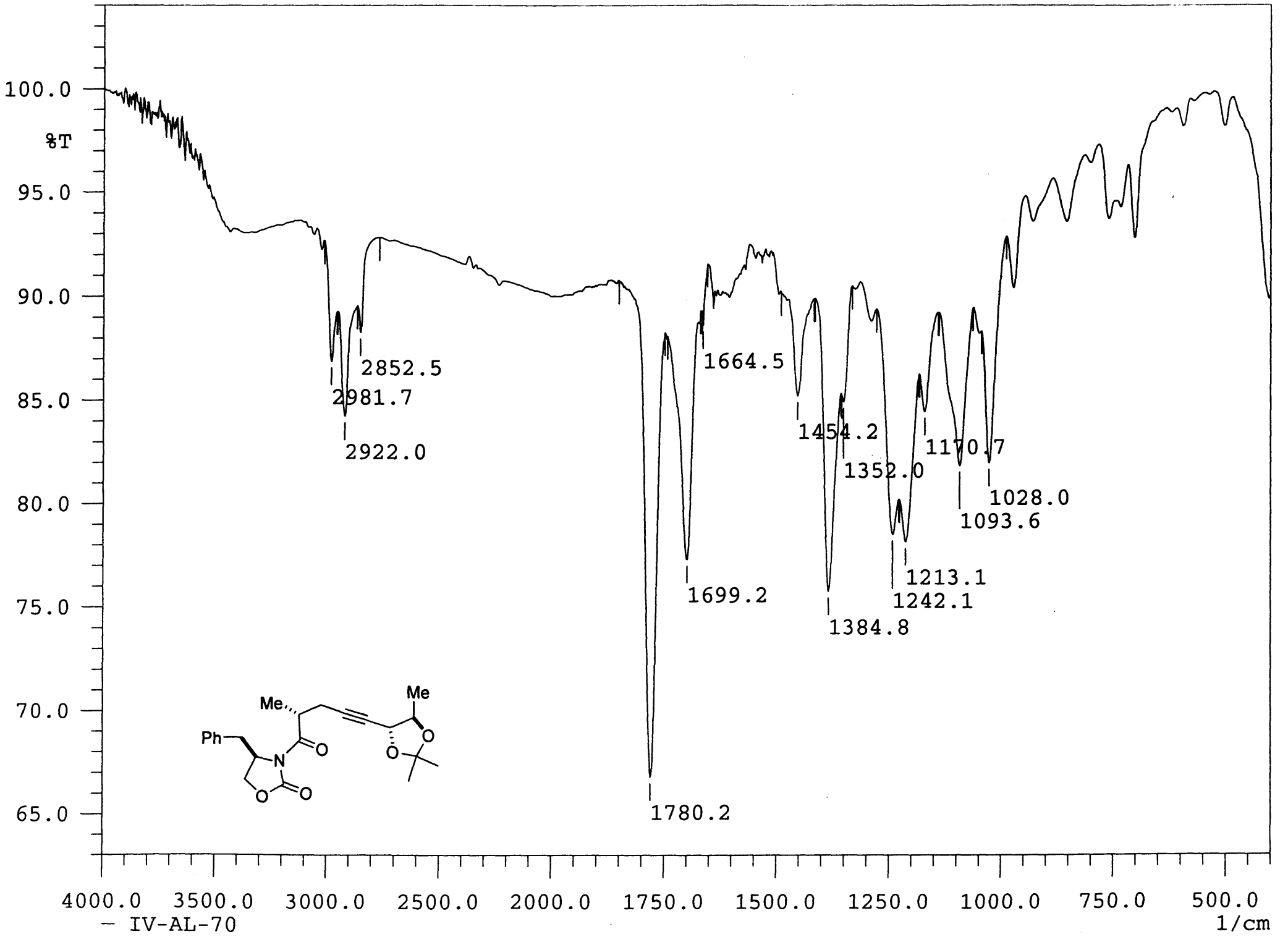


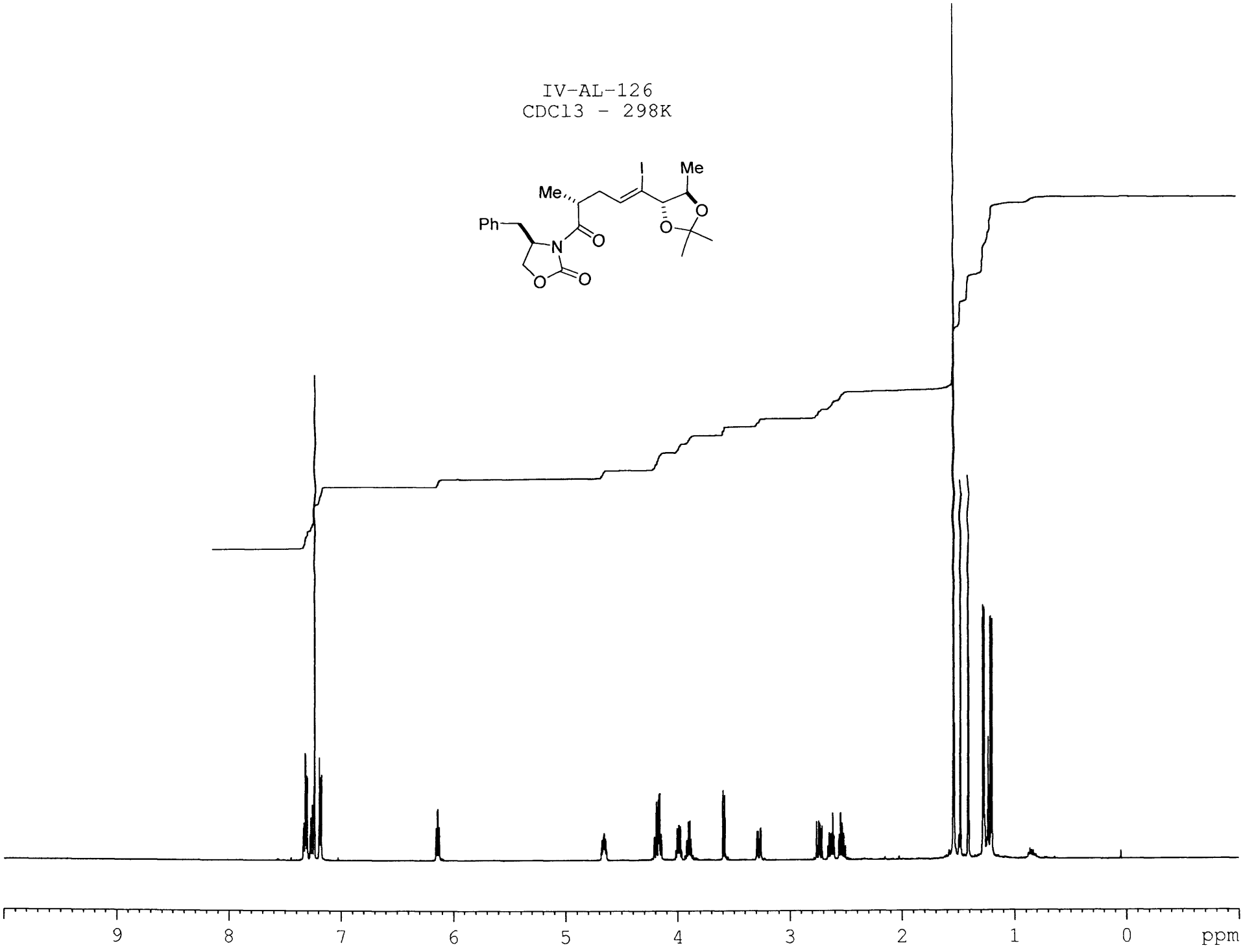


IV-AL-70
HMBC
CDCl3 - 298K

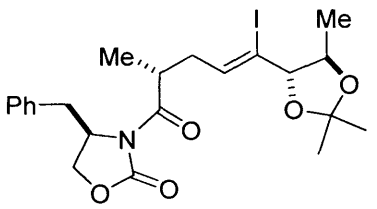


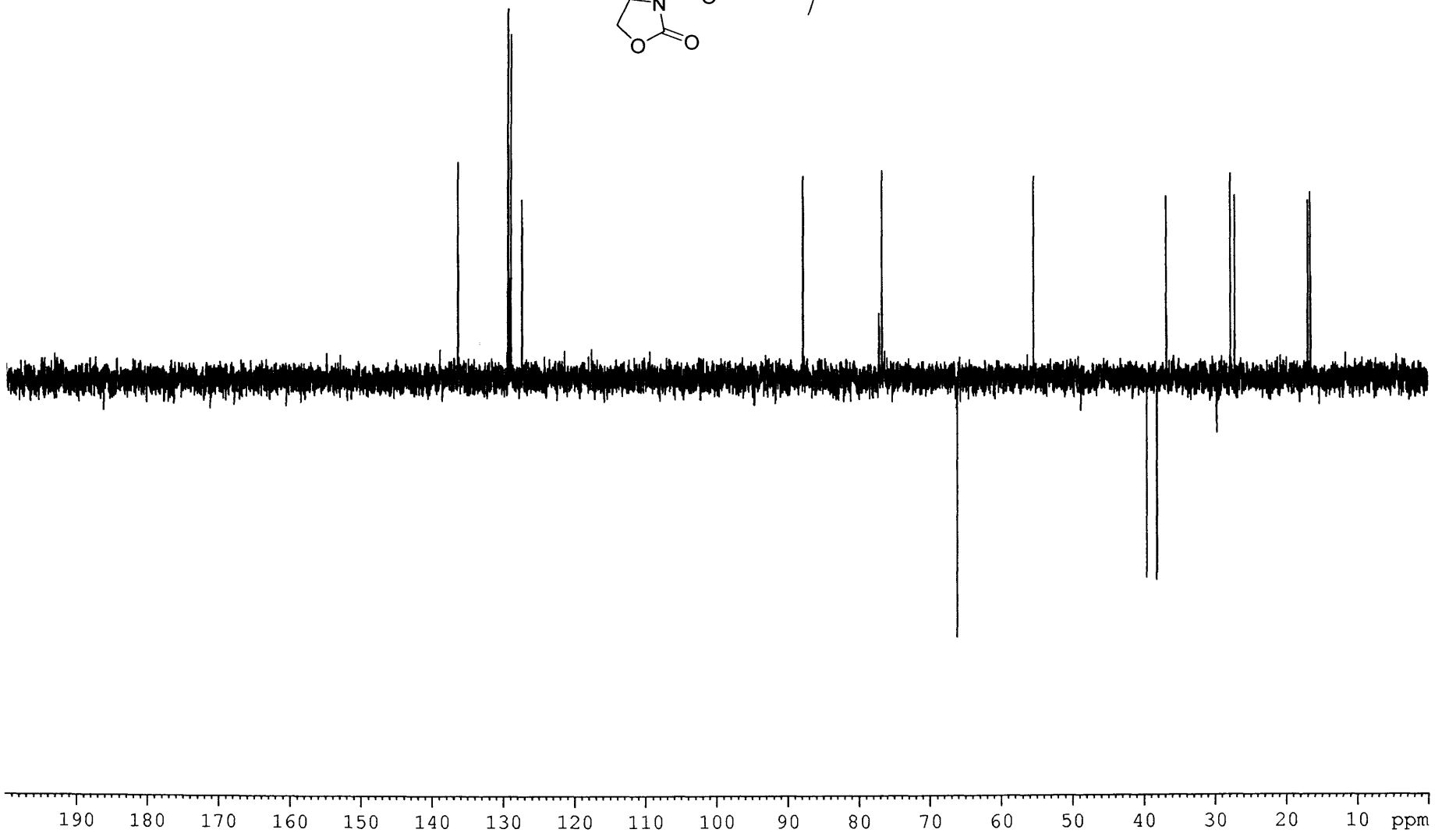

02131006: Scan 49 (9.70 min) - Back
Base: 408.00 Int: 5.26814e+006 Sample: VG 70-SE Positive Ion FAB
Sample: IV-AL-70
Instrument Resolution: 10,000
Theoretical Mass (C22H27NO5): 408.17868 (M+Na)
Measured Mass: 408.178770
Error: 0.22ppm
Me
Me
Ph
N
O
O
O
O
O
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
408
178
222
328
370
464
536
558
584
100
150
200
250
300
350
400
450
500
550
600
650
700
750
m/z


100.0
%T
95.0
90.0
85.0
80.0
75.0
70.0
65.0
2852.5
2981.7
2922.0
1664.5
1454.2
1352.0
1170.7
1028.0
1093.6
1699.2
1213.1
1242.1
1384.8
1780.2
Me
Me
Ph
N
O
O
O
O
O
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
- IV-AL-70
1/cm

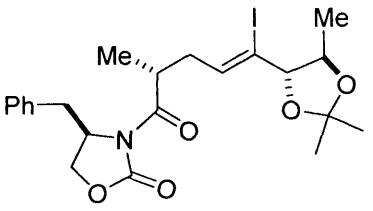

IV-AL-126
CDCl3 - 298K
Me
I
Me
Ph
N
O
O
O
O
O
9
8
7
6
5
4
3
2
1
0
ppm

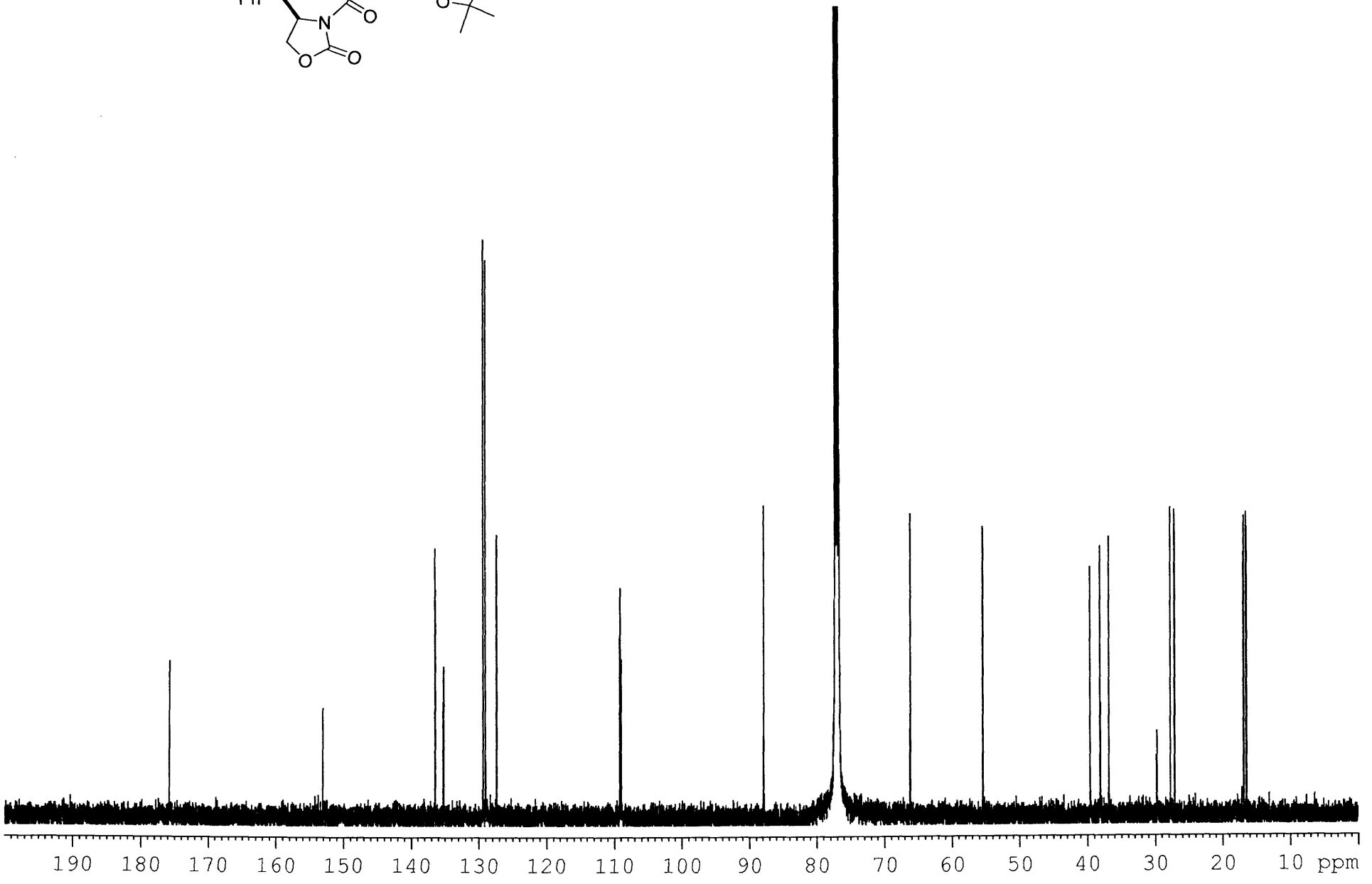
IV-AL-126
DEPT
CDCl3 - 298K

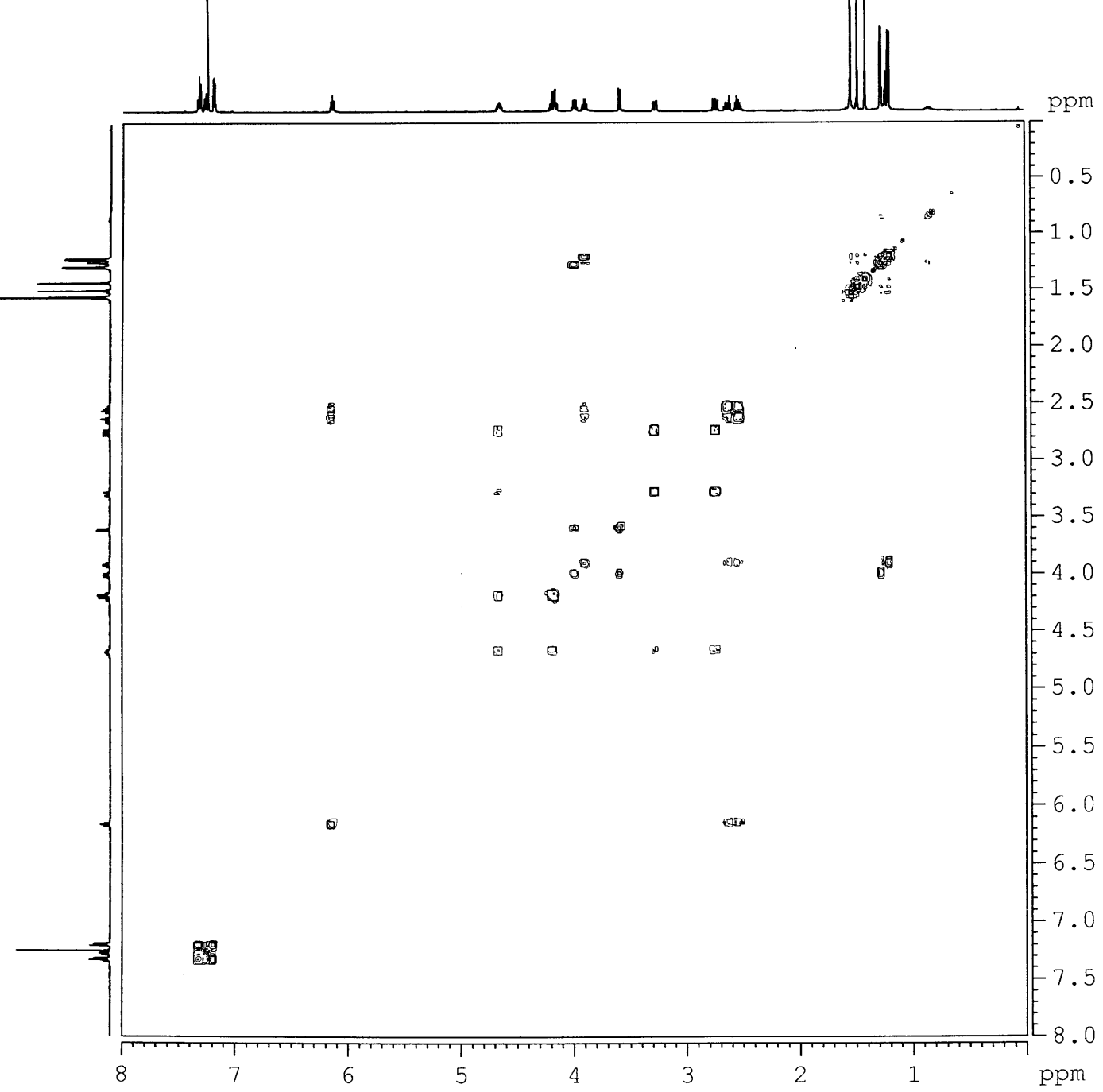




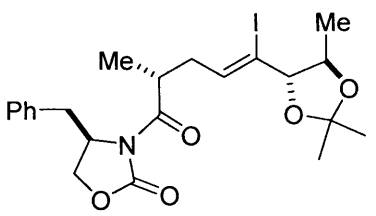
IV-AL-126
13C
CDCl3 - 298K

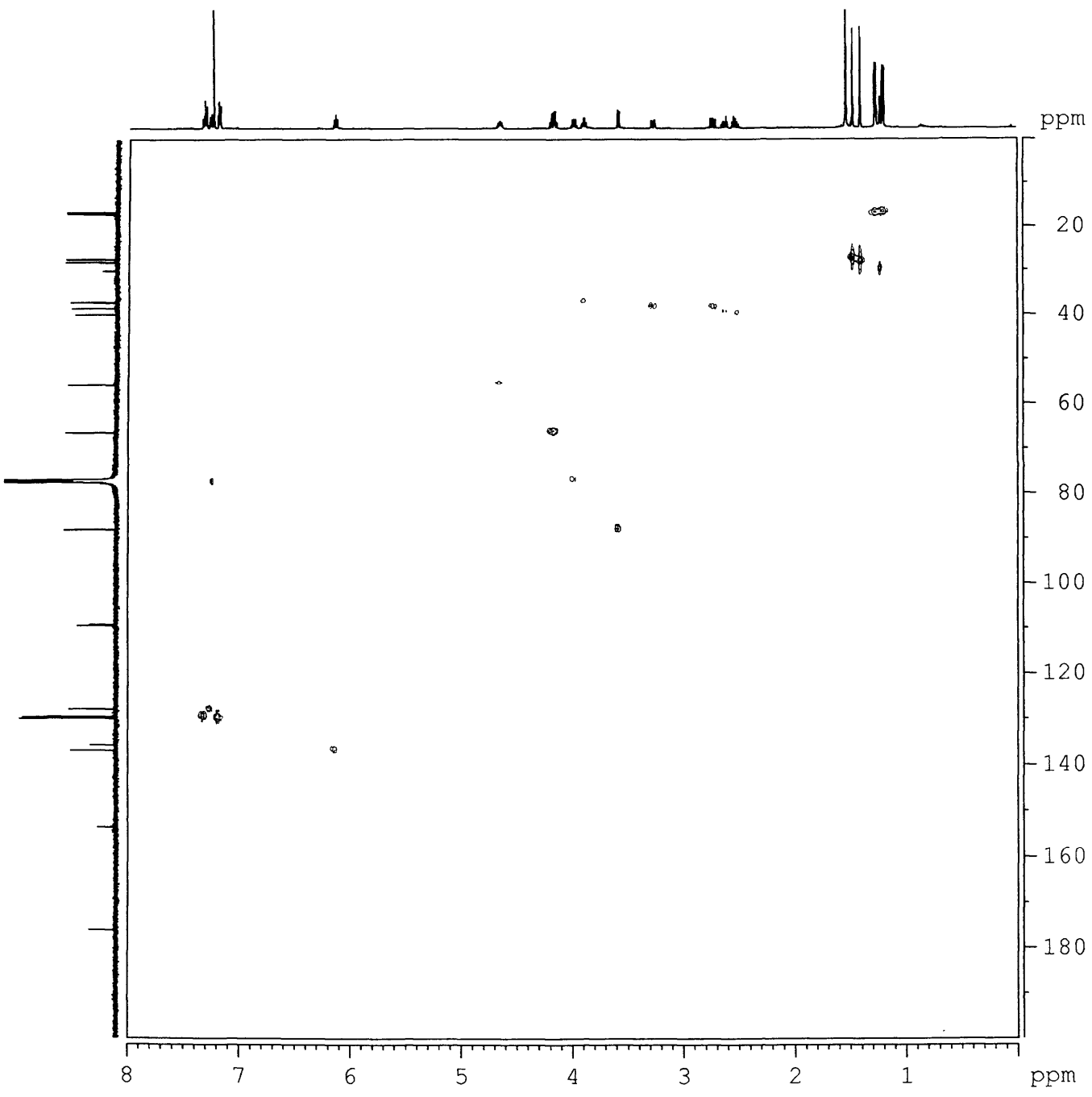




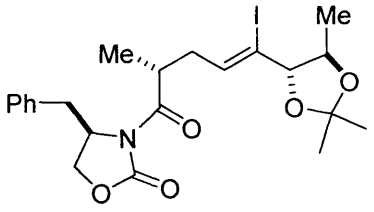


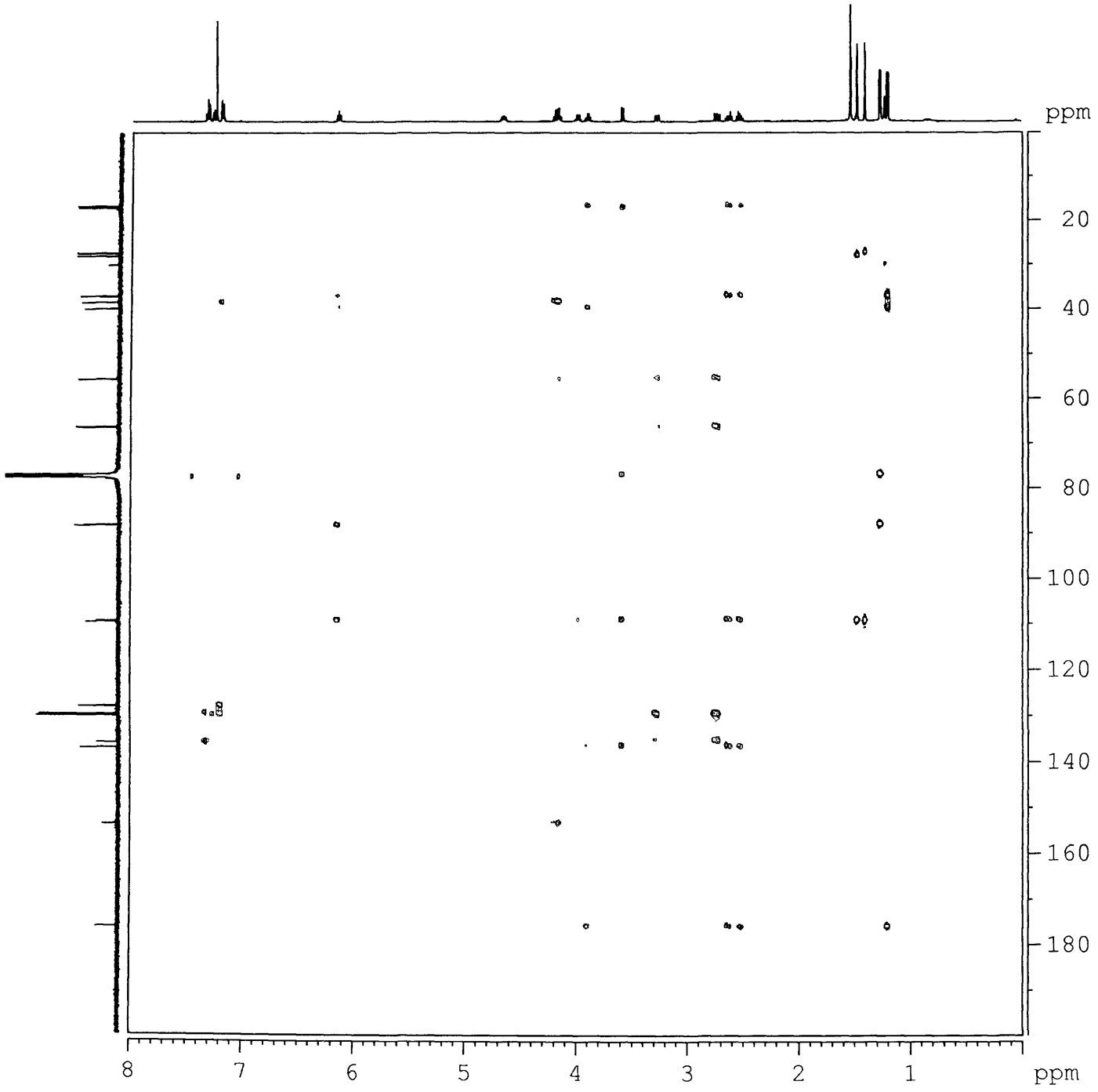
IV-AL-126
COSY
CDCl3 - 298K



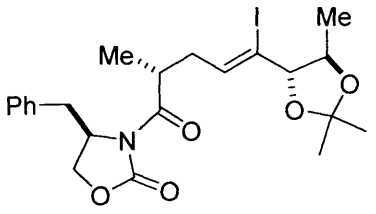


IV-AL-126
HMQC
CDCl3 - 298K

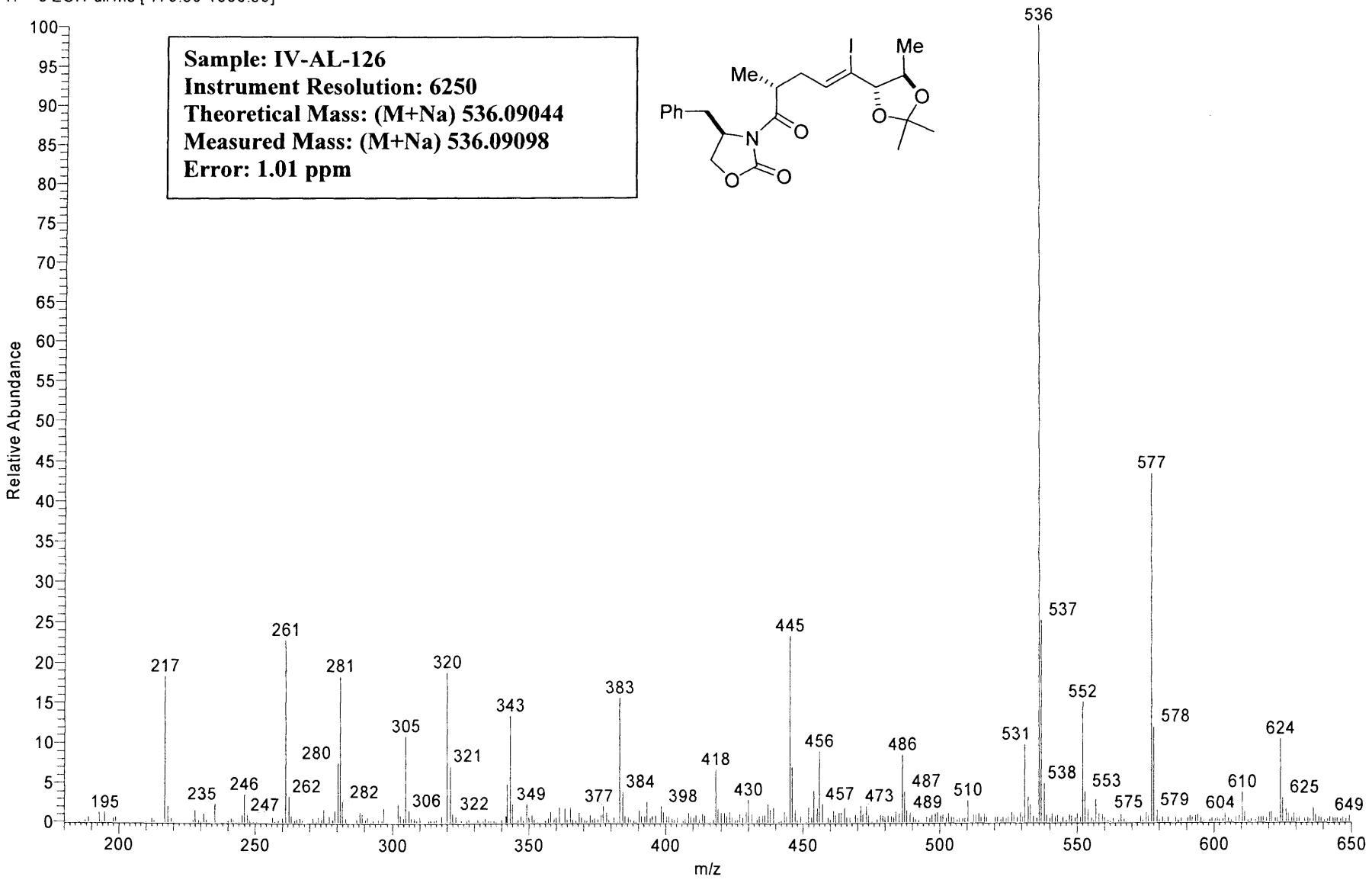


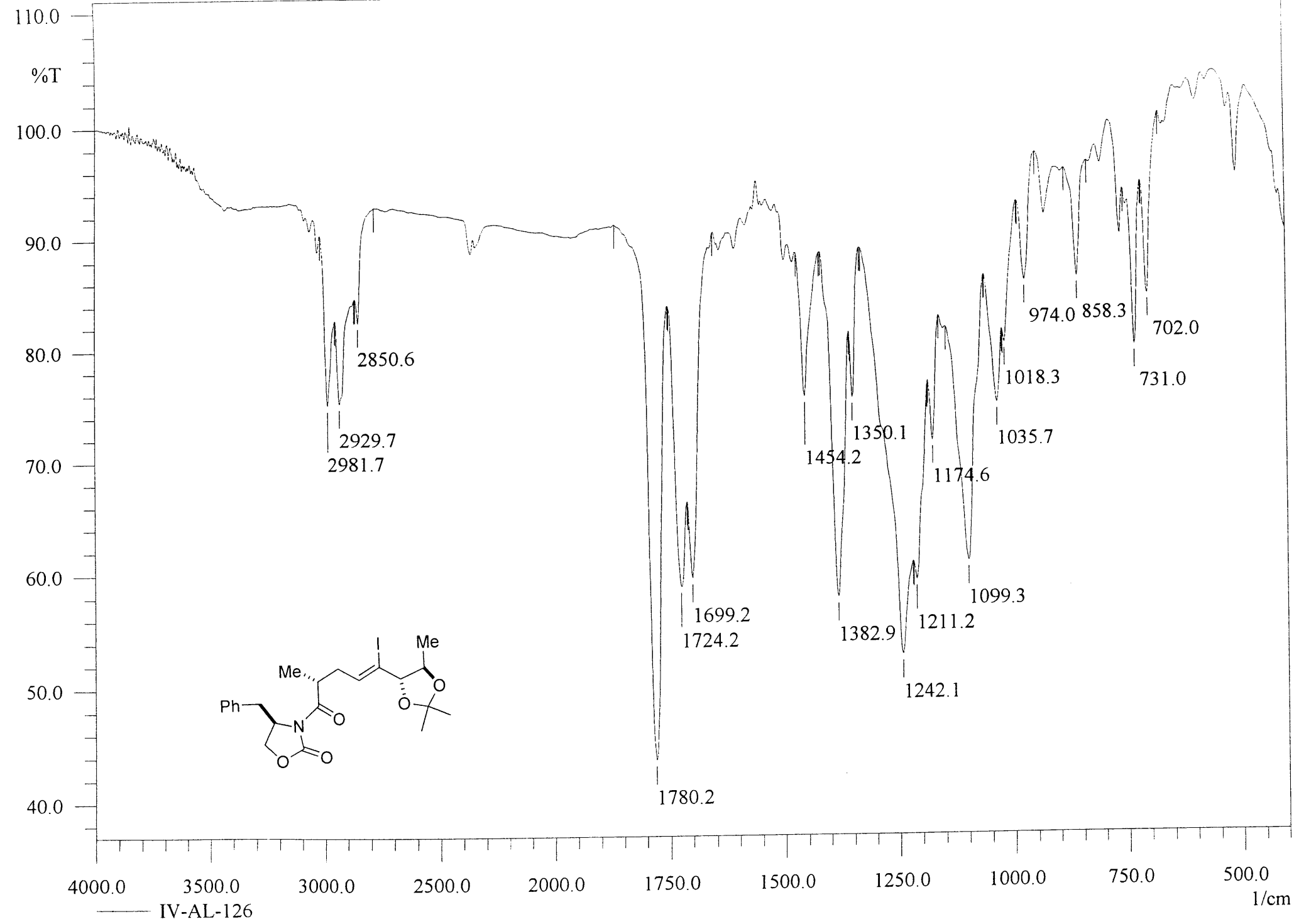


IV-AL-126
HMBC
CDCl3 - 298K

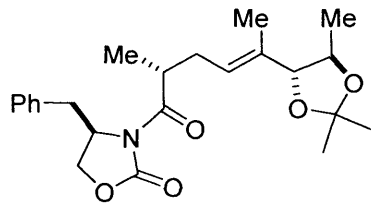


rjf494 #475 RT: 19.50 AV: 1 SB: 384 0.42-18.08 , 19.70-20.02 NL: 3.41E6
T: + c ESI Full ms [179.50-1000.50]

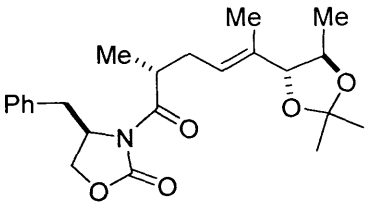


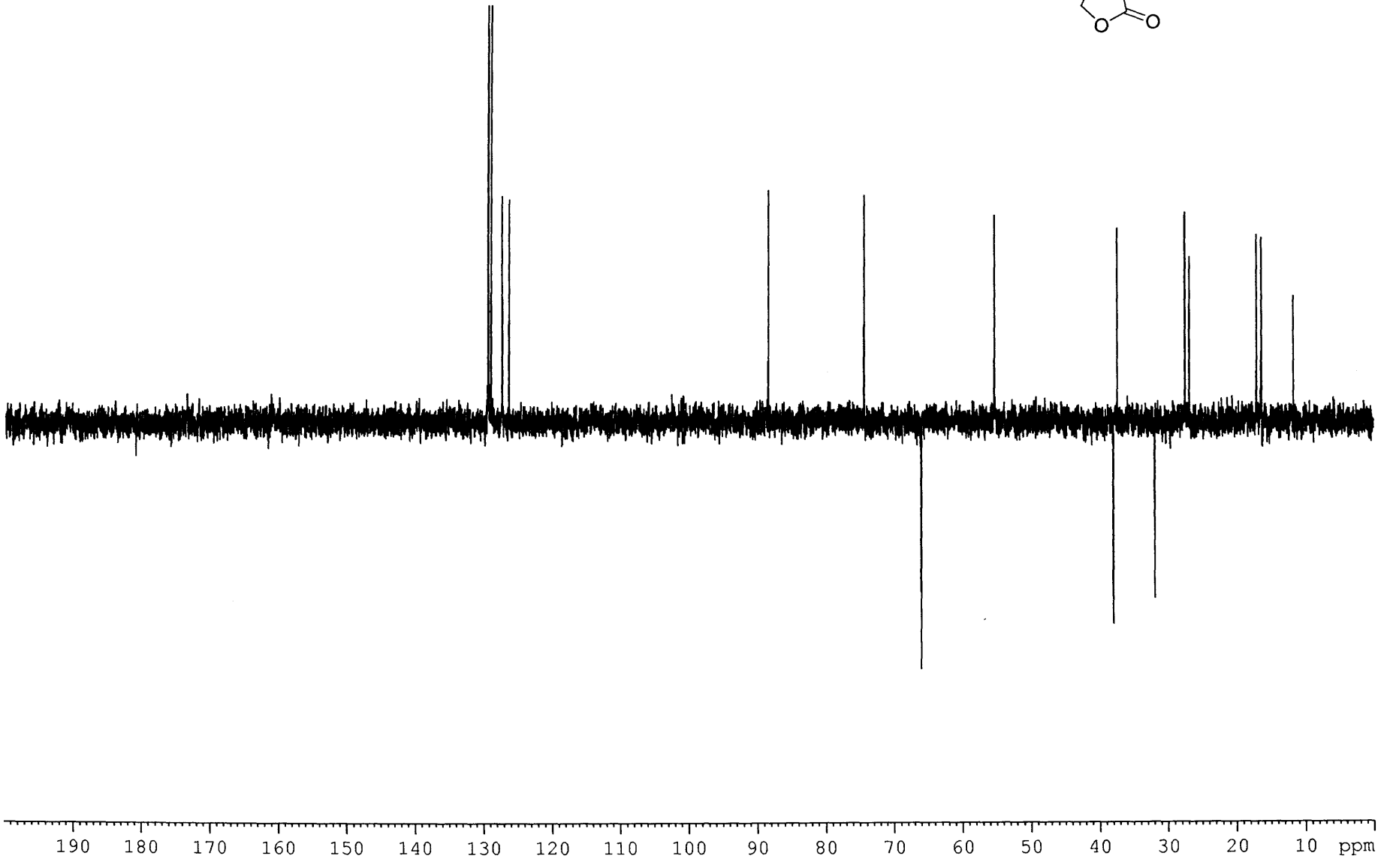

110.0
%T
100.0
90.0
80.0
70.0
60.0
50.0
40.0
2850.6
2929.7
2981.7
1699.2
1724.2
1780.2
1454.2
1350.1
1382.9
1242.1
1211.2
1174.6
1099.3
1035.7
1018.3
974.0
858.3
731.0
702.0
Me
Me
Ph
N
O
O
O
O
O
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
IV-AL-126

IV-AL-128
CDCl3 - 298K

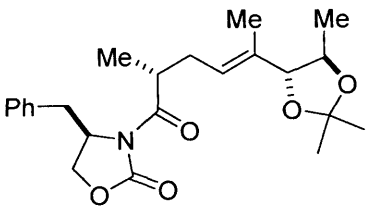


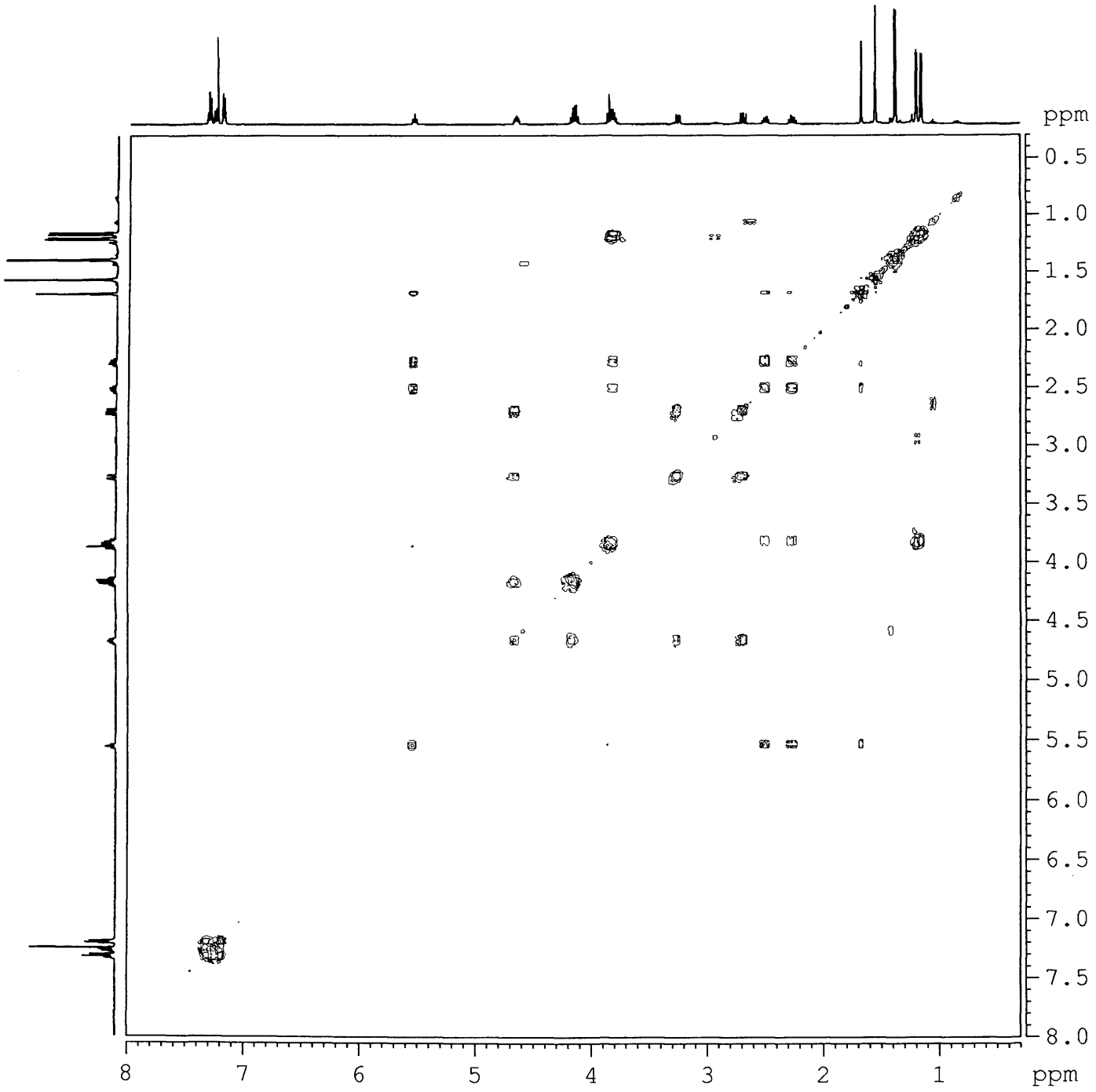
IV-AL-128
DEPT
CDCl3 - 298K



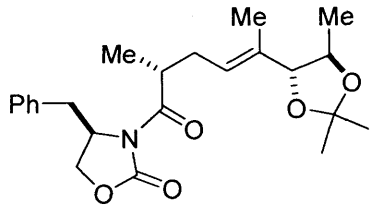


IV-AL-128
13C
CDCl3 - 298K

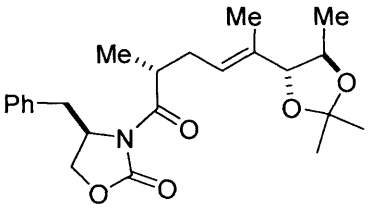


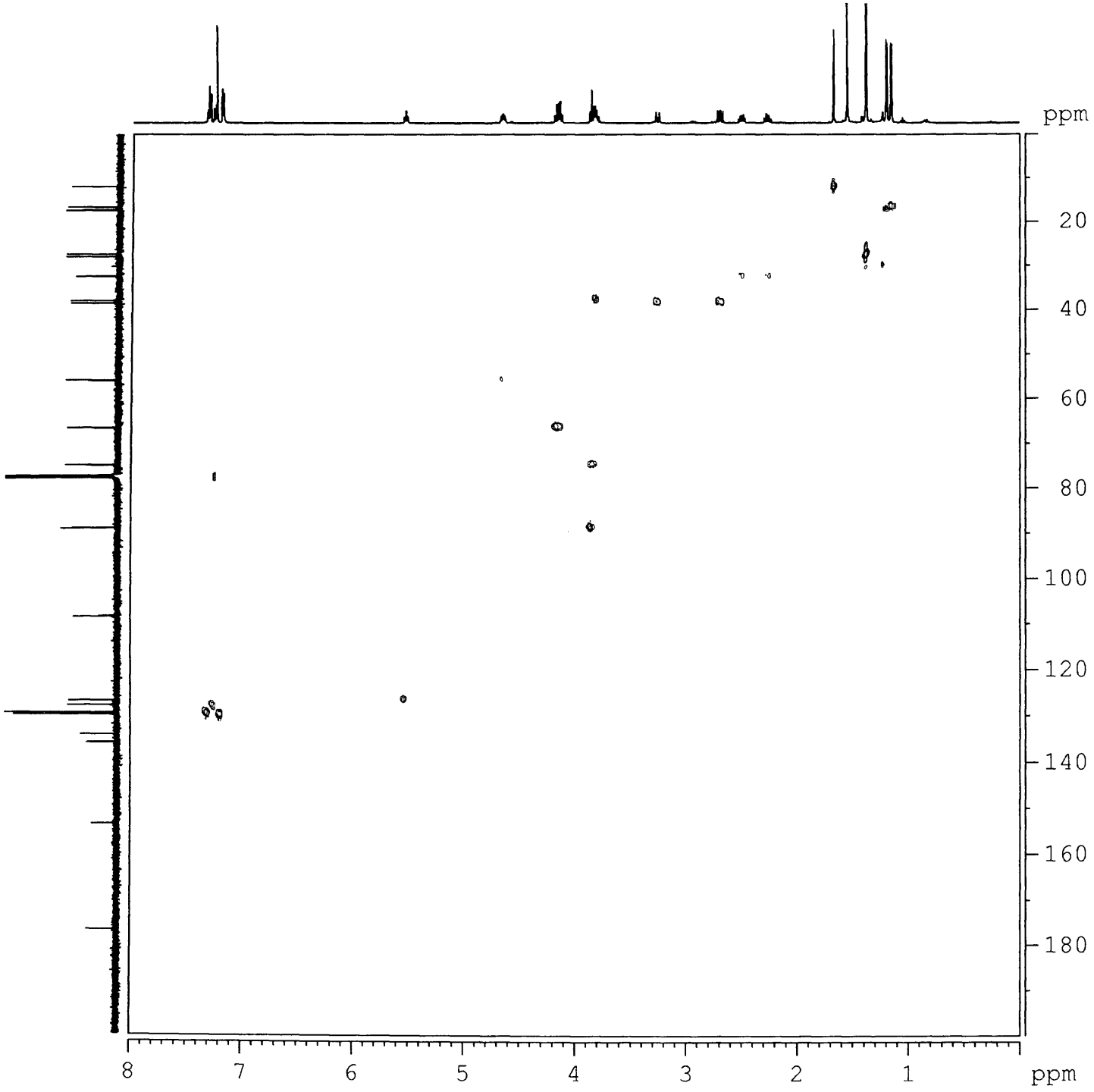


IV-AL-128
COSY
CDCl3 - 298K

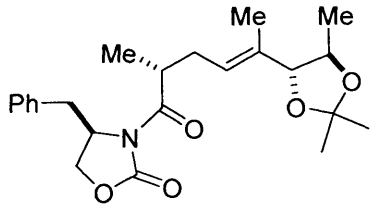


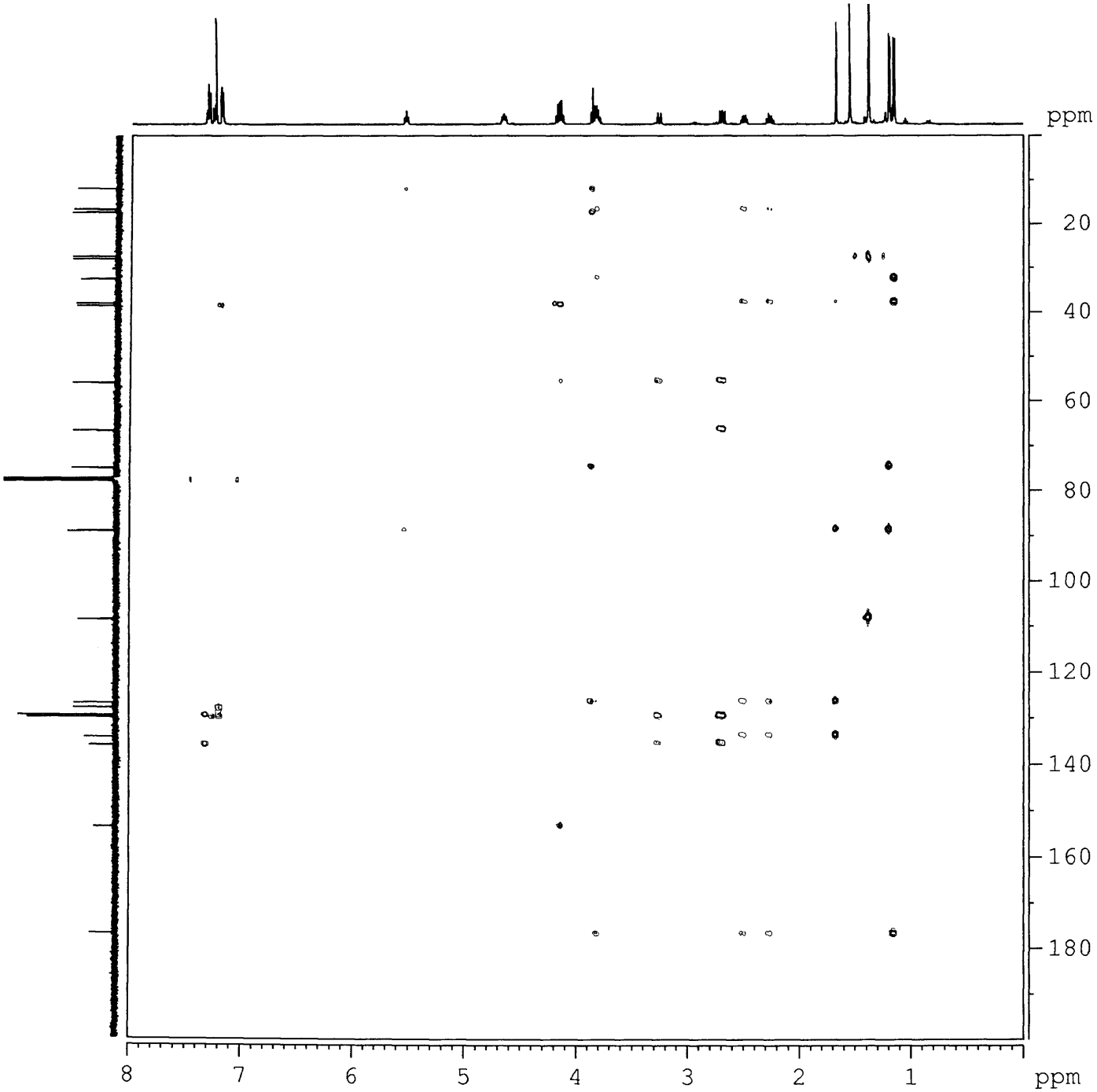
IV-AL-128
HMQC
CDCl3 - 298K

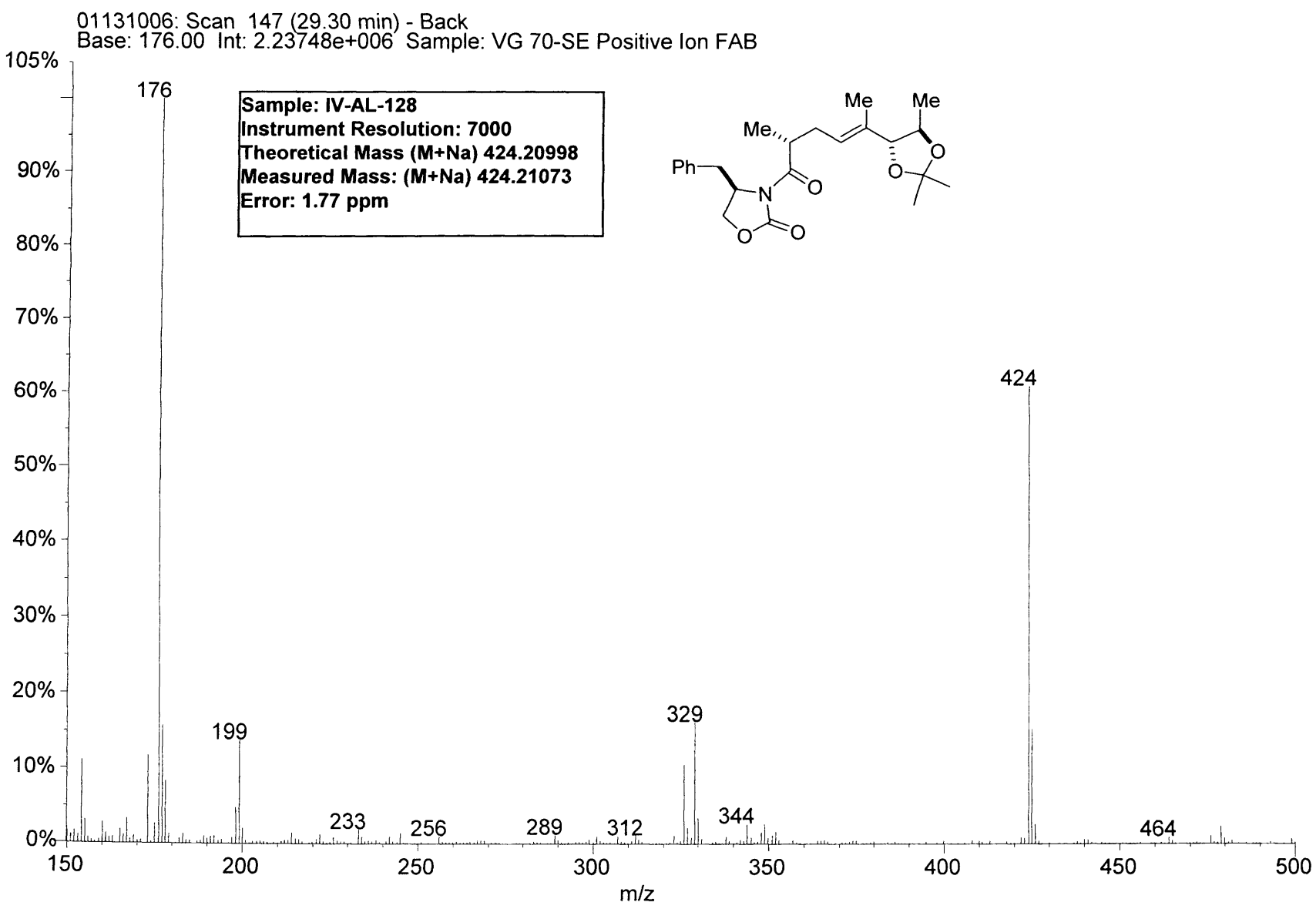


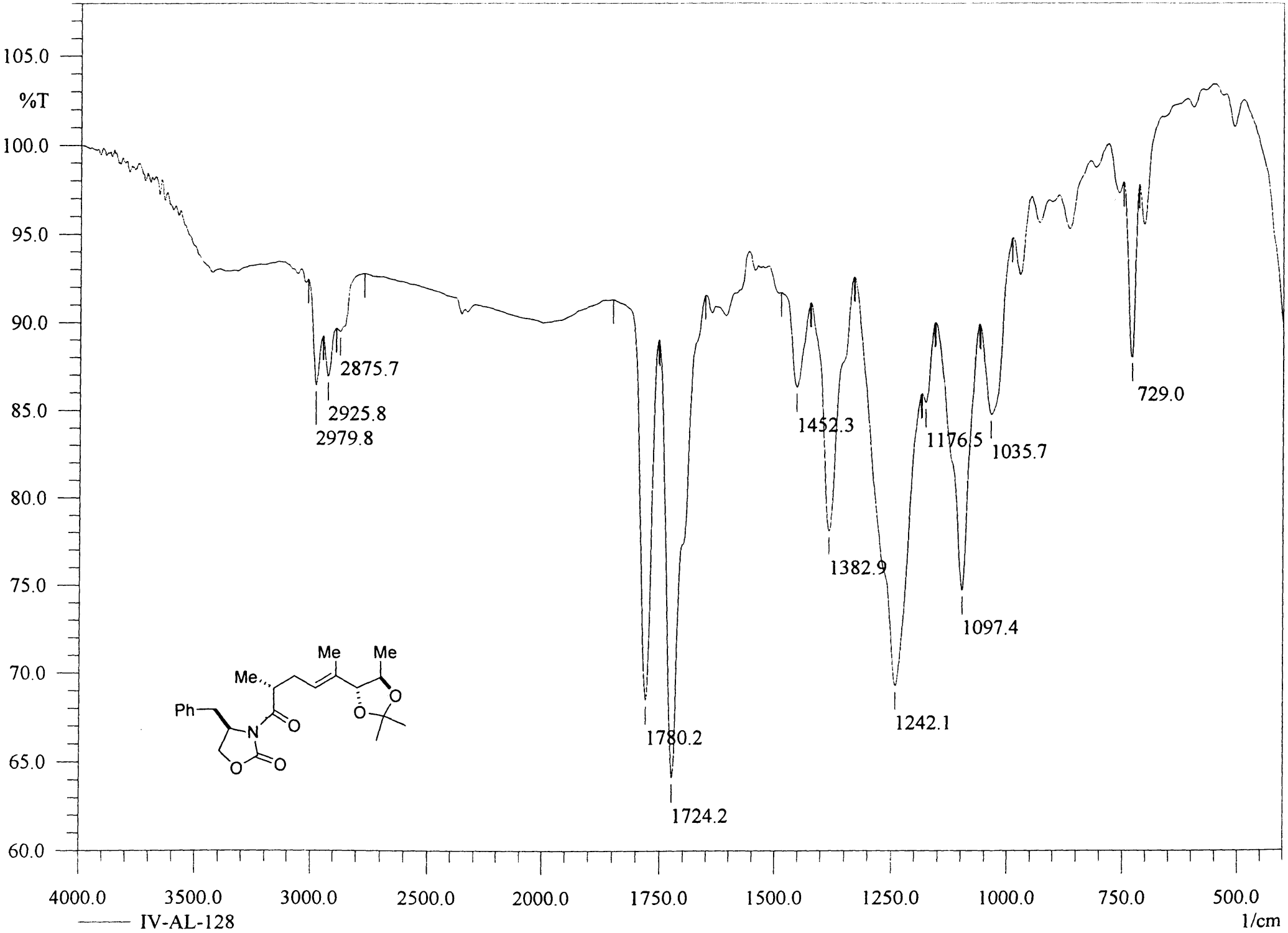


IV-AL-128
HMBC
CDCl3 - 298K

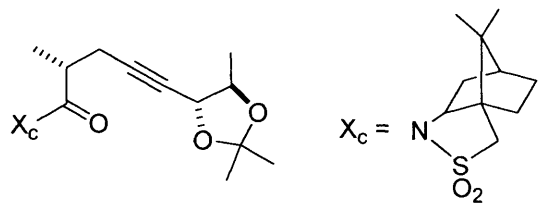




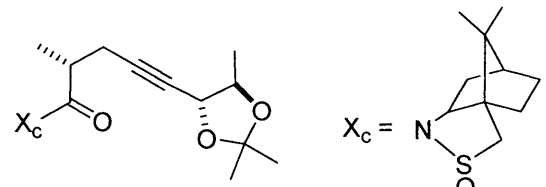

01131006: Scan 147 (29.30 min) - Back
Base: 176.00 Int: 2.23748e+006 Sample: VG 70-SE Positive Ion FAB
Sample: IV-AL-128
Instrument Resolution: 7000
Theoretical Mass (M+Na) 424.20998
Measured Mass: (M+Na) 424.21073
Error: 1.77 ppm
Me
Me
Me
Ph
N
O
O
O
O
O
105%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
176
199
233
256
289
312
329
344
424
464
150
200
250
300
350
400
450
500
m/z


105.0
%T
100.0
95.0
90.0
85.0
80.0
75.0
70.0
65.0
60.0
2875.7
2925.8
2979.8
1780.2
1724.2
1452.3
1382.9
1242.1
1176.5
1097.4
1035.7
729.0
Me
Me
Me
Ph
N
O
O
O
O
O
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
IV-AL-128
1/cm

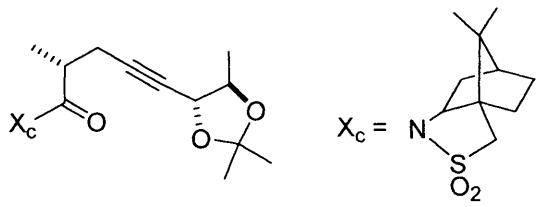
IV-AL-162
CDCl3 - 298K

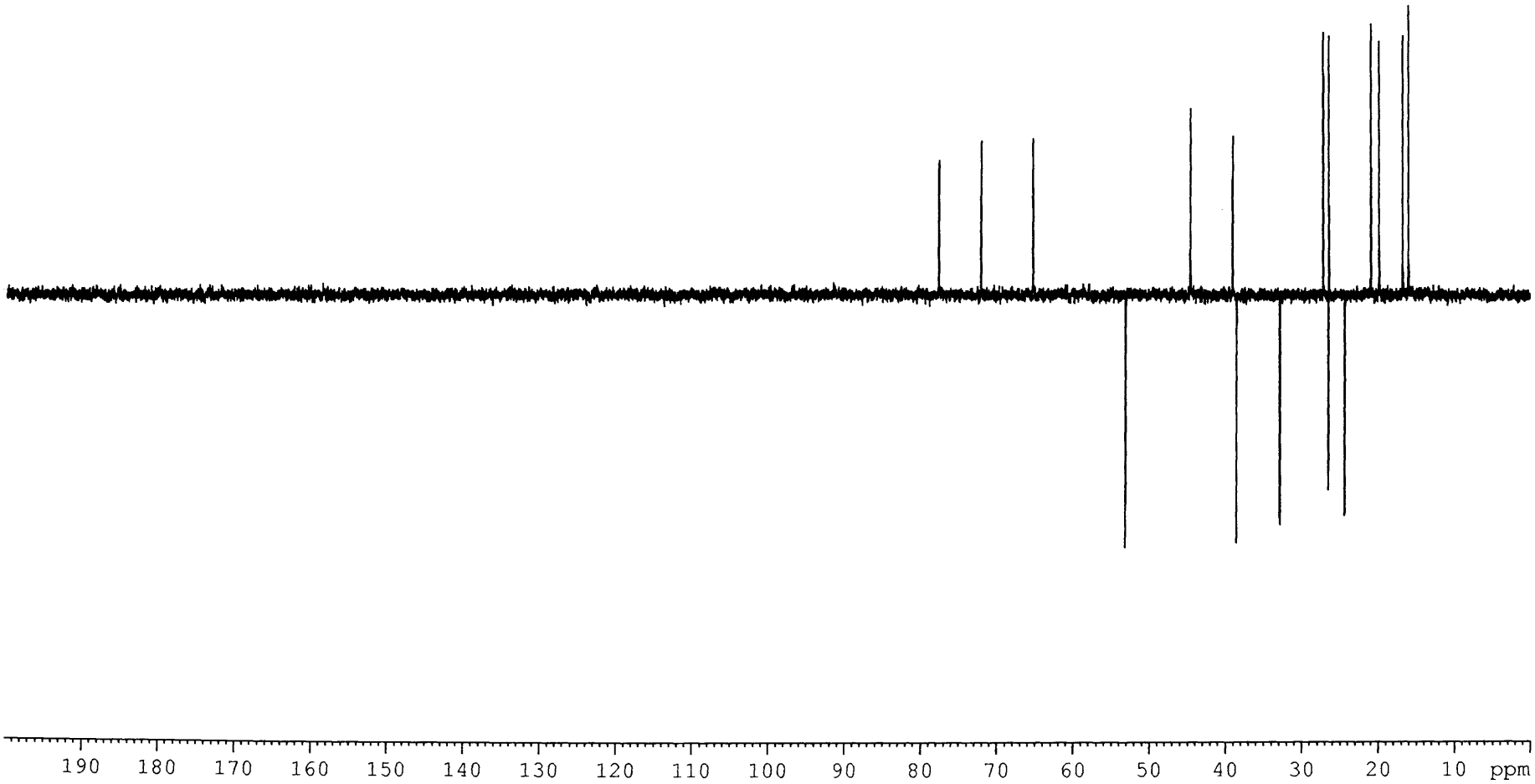


IV-AL-162
CDCl3 - 298K

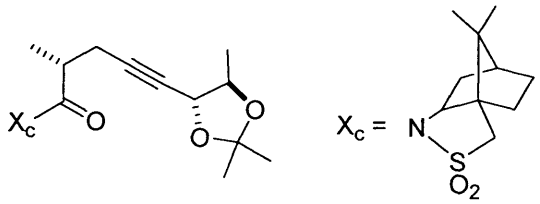


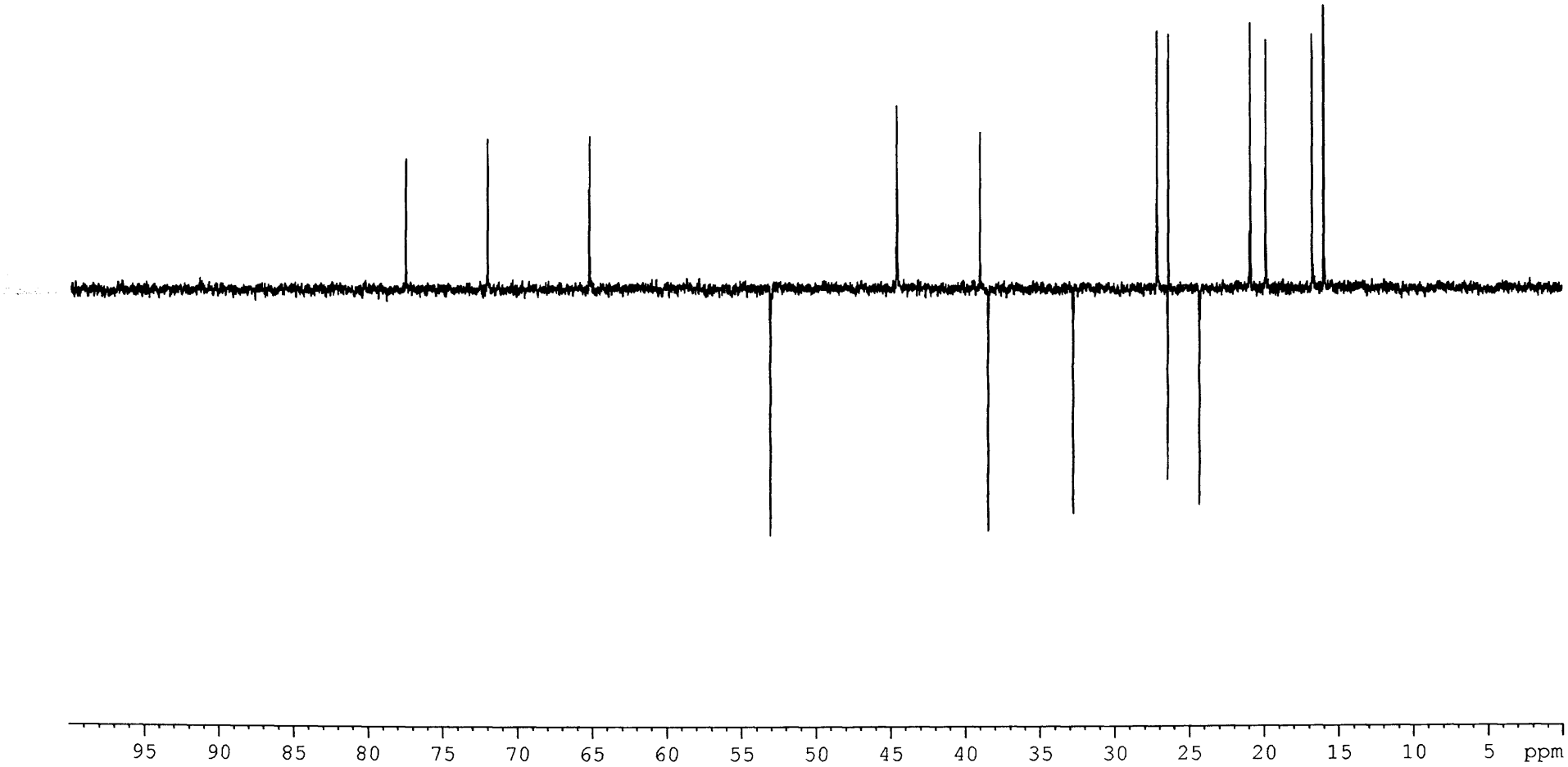
IV-AL-162
DEPT
CDCl3 - 298K

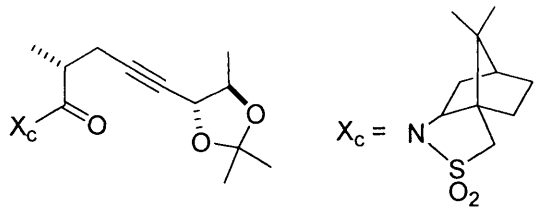




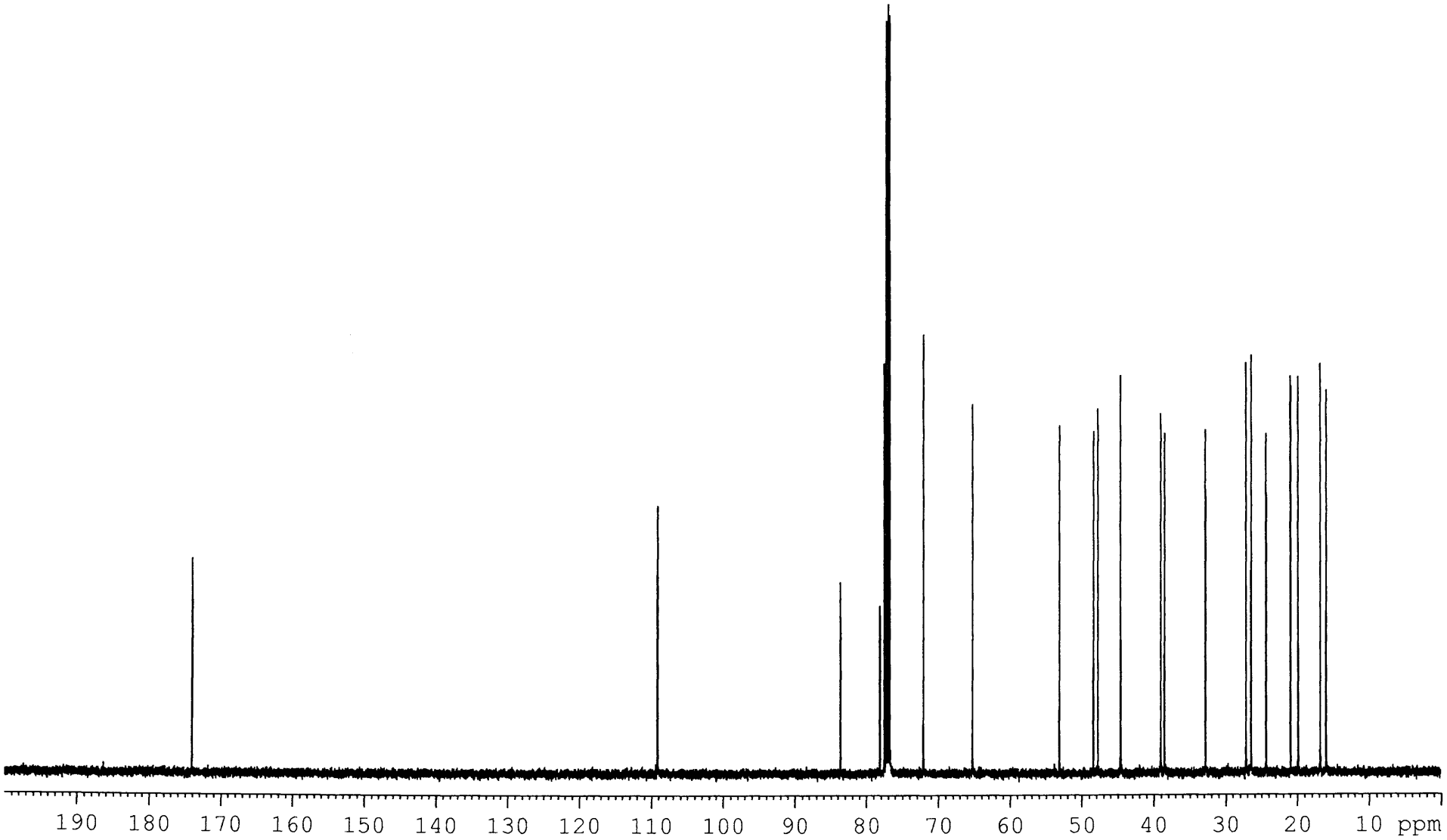
IV-AL-162
DEPT
CDCl3 - 298K

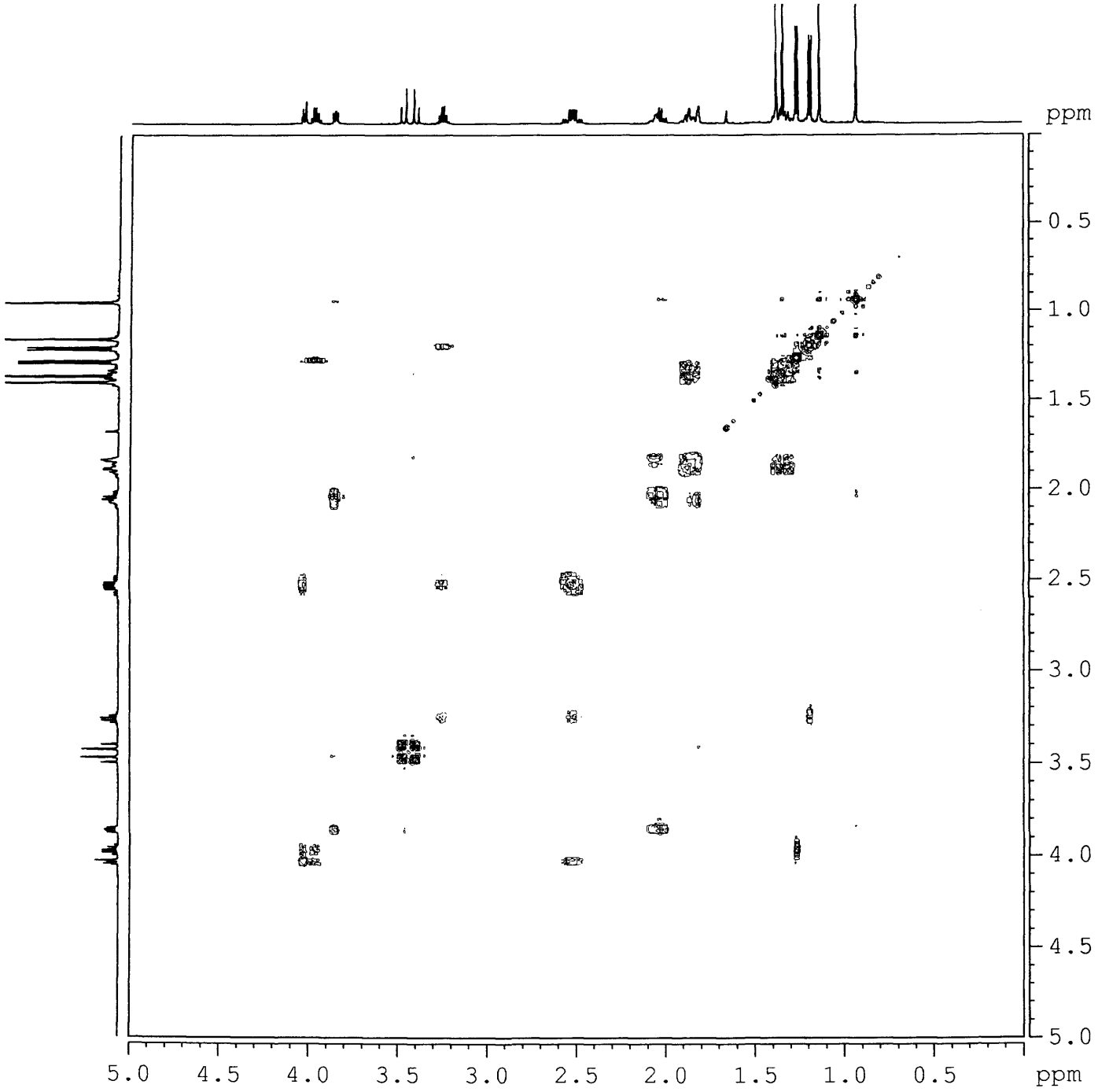




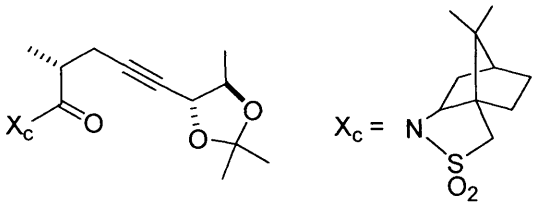


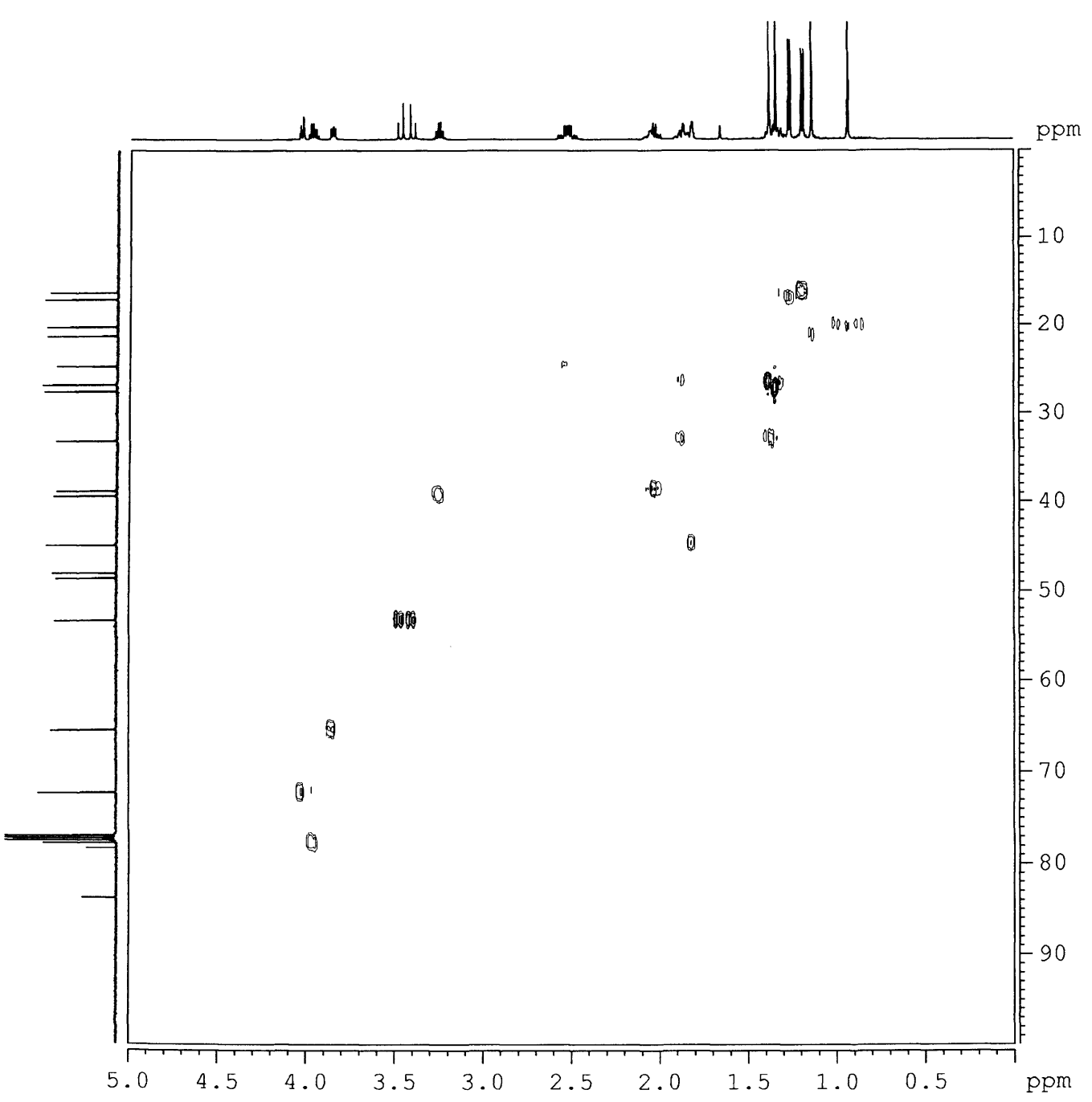
IV-AL-162
13C
CDCl3 - 298K



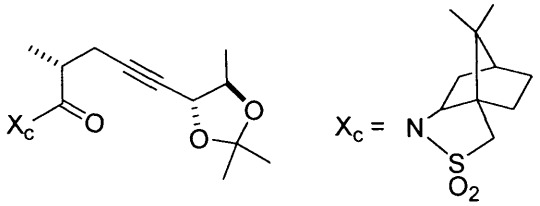


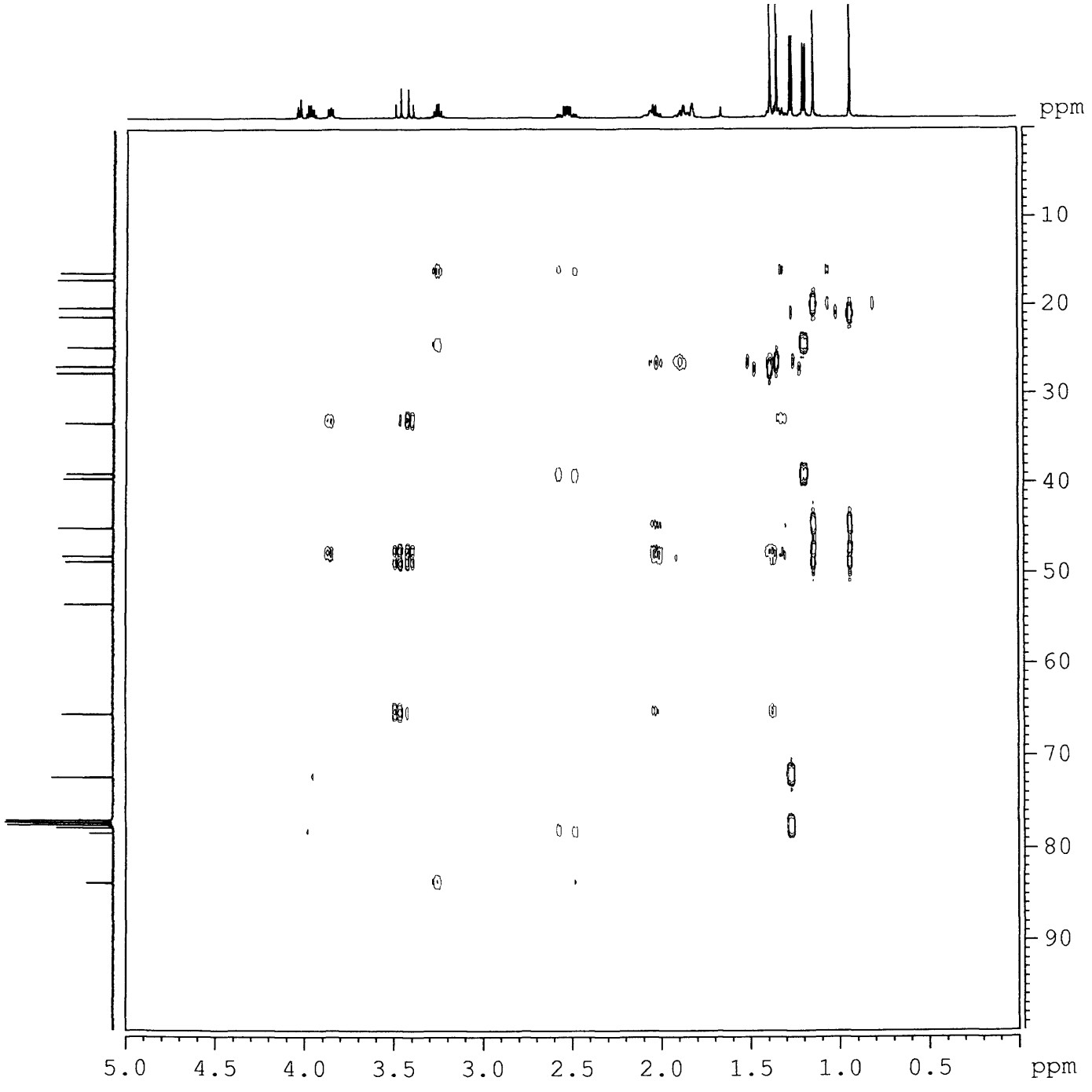
IV-AL-162
COSY
CDCl3 - 298K



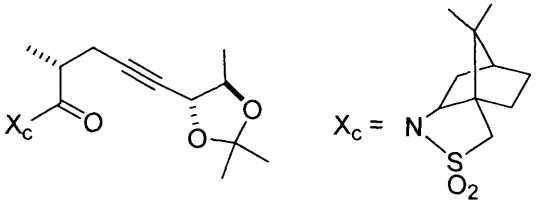


IV-AL-162
HMQC
CDCl3 - 298K

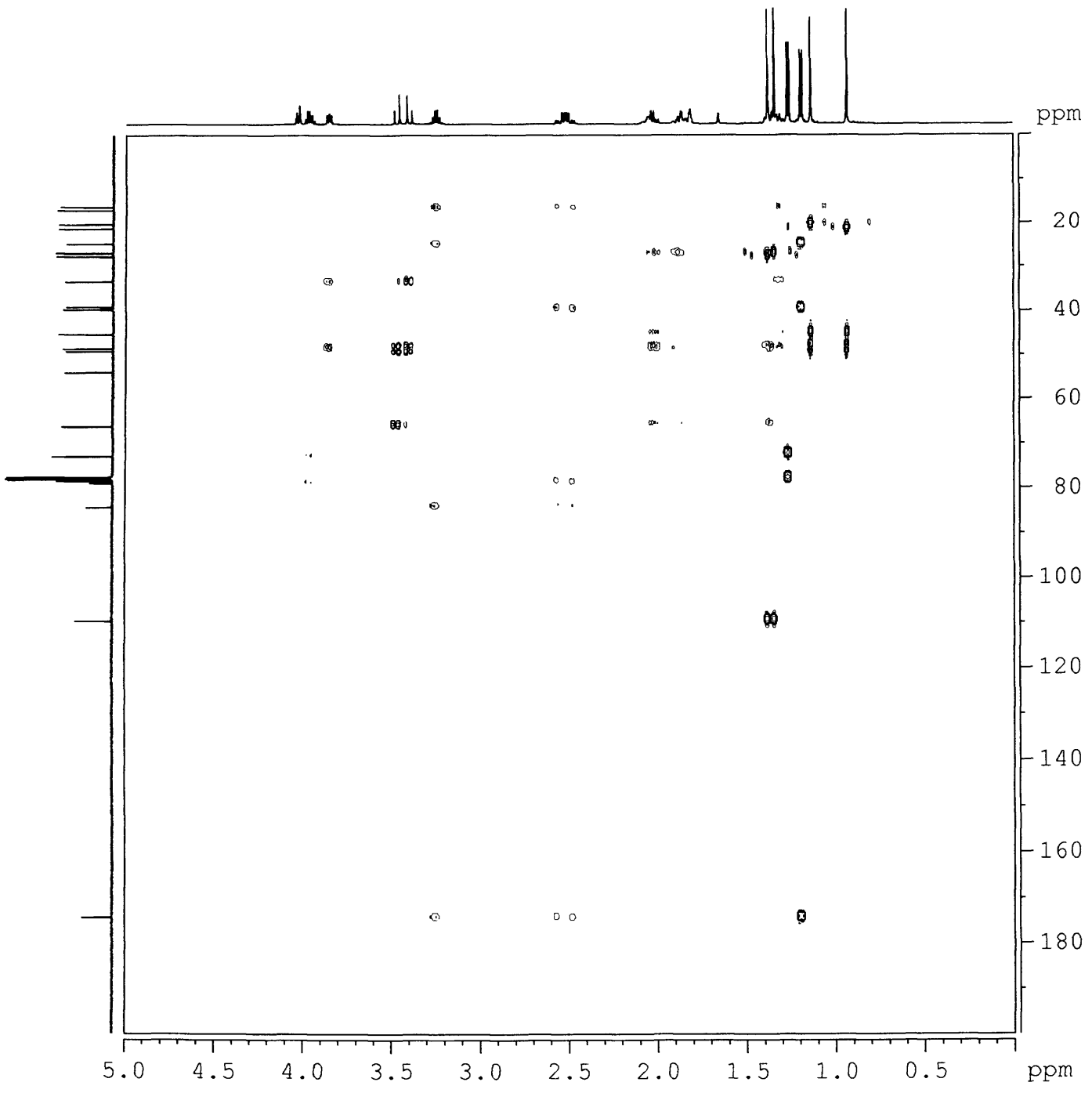


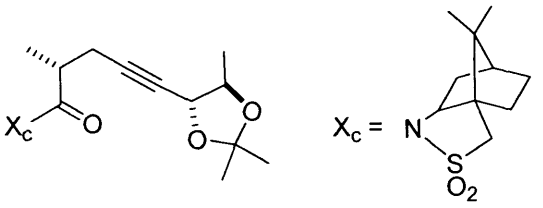


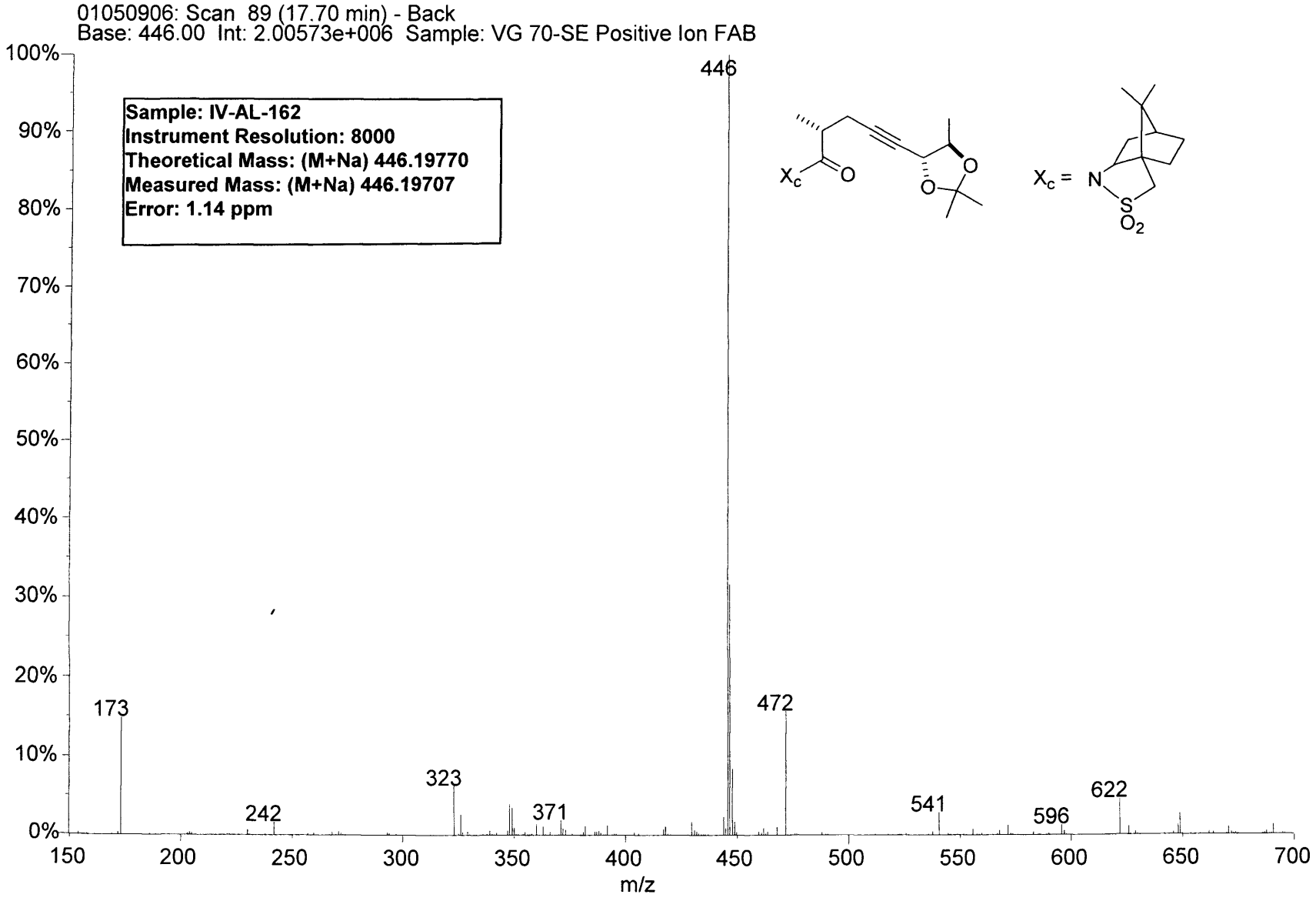
IV-AL-162
HMBC
CDC13 - 298K

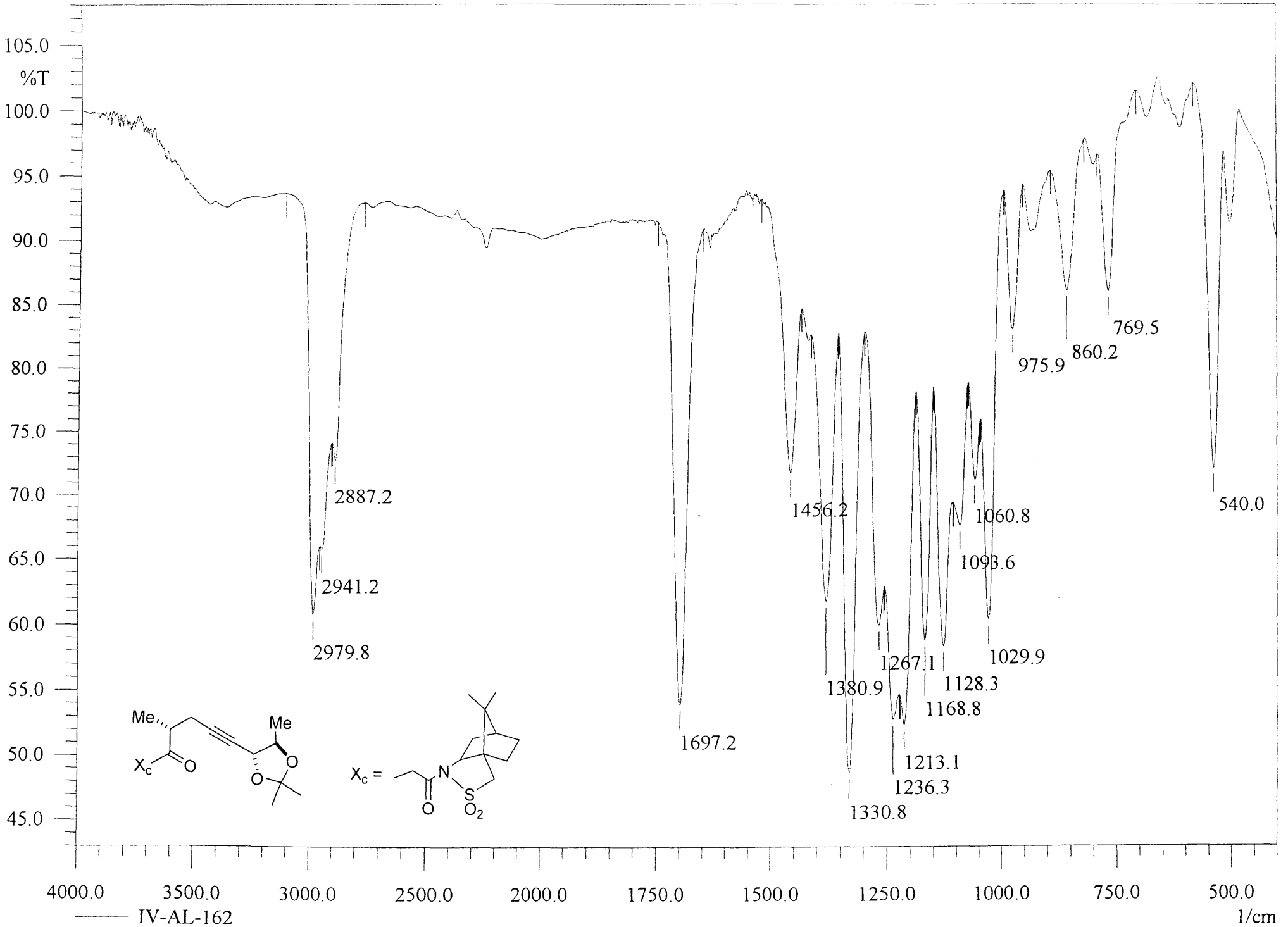


IV-AL-162
HMBC
CDCl3 - 298K

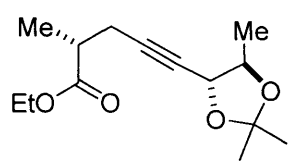




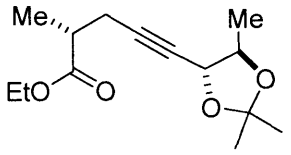

01050906: Scan 89 (17.70 min) - Back
Base: 446.00 Int: 2.00573e+006 Sample: VG 70-SE Positive Ion FAB
Sample: IV-AL-162
Instrument Resolution: 8000
Theoretical Mass: (M+Na) 446.19770
Measured Mass: (M+Na) 446.19707
Error: 1.14 ppm
Xc
O
O
O
Xc =
N
S
O2
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
446
472
173
323
242
371
541
596
622
150
200
250
300
350
400
450
500
550
600
650
700
m/z

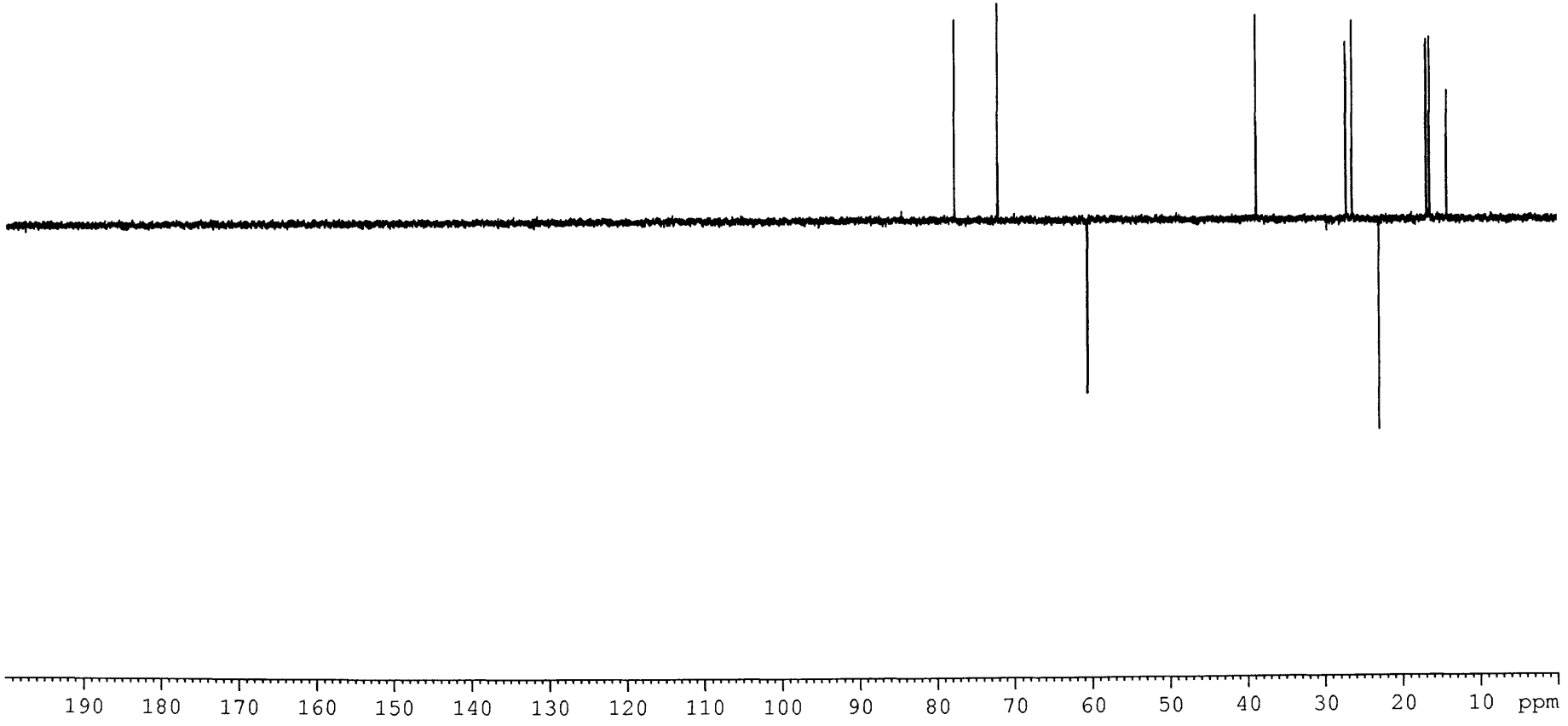

105.0
%T
100.0
95.0
90.0
85.0
80.0
75.0
70.0
65.0
60.0
55.0
50.0
45.0
2887.2
2941.2
2979.8
1697.2
1456.2
1380.9
1330.8
1267.1
1236.3
1213.1
1168.8
1128.3
1093.6
1060.8
1029.9
975.9
860.2
769.5
540.0
Me
Me
Xc
O
O
O
Xc =
N
S
O
O2
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
IV-AL-162

IV-AL-150
CDCl3 - 298K

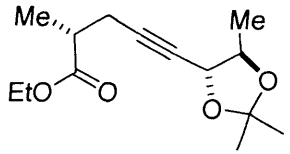


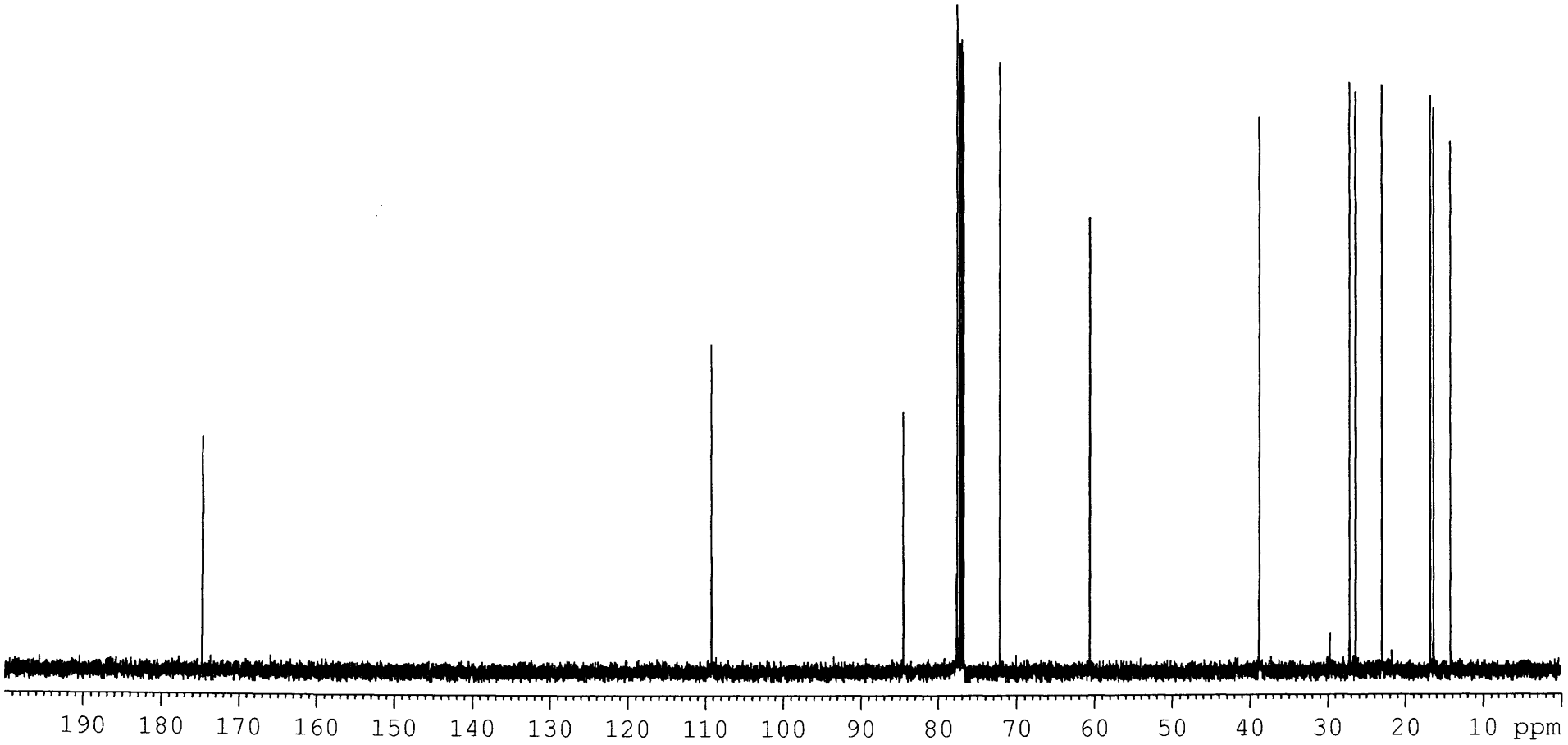
IV-AL-150
DEPT
CDCl3 - 298K

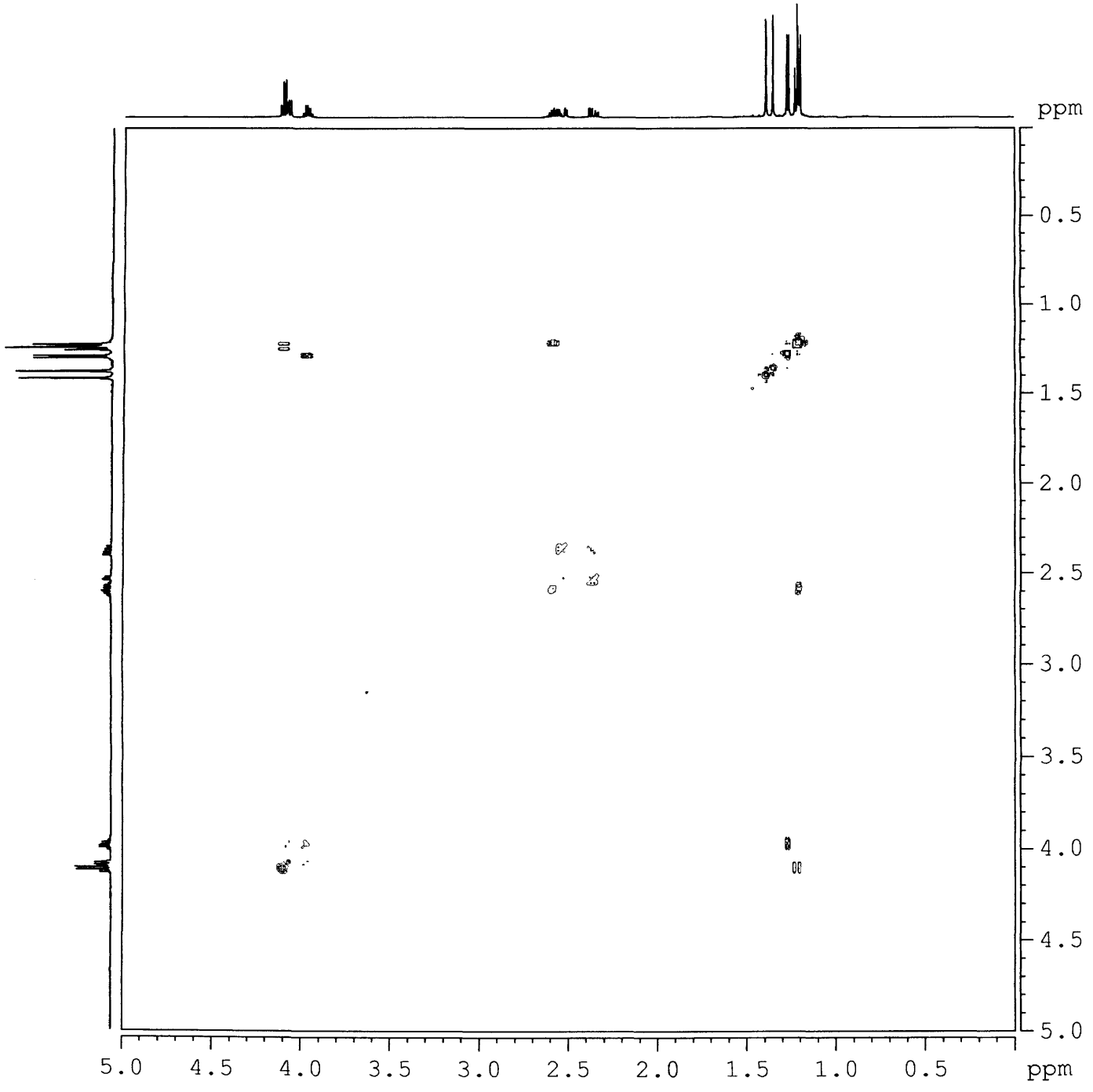




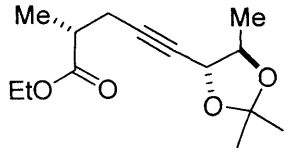
IV-AL-150
13C
CDCl3 - 298K

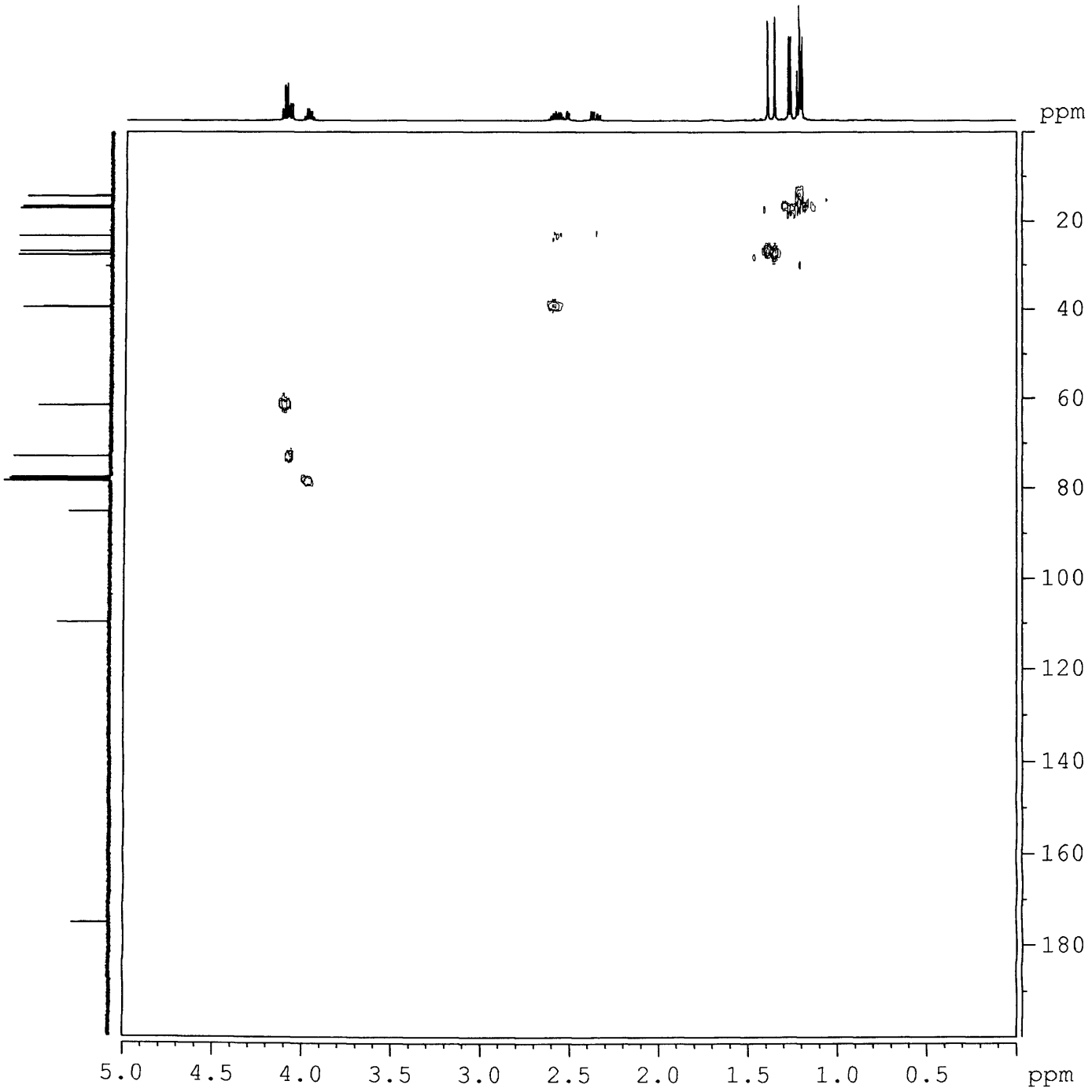




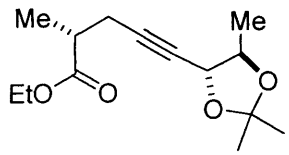


IV-AL-150
COSY
CDCl3 - 298K

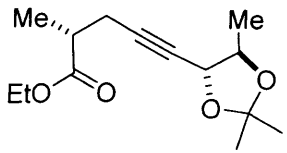


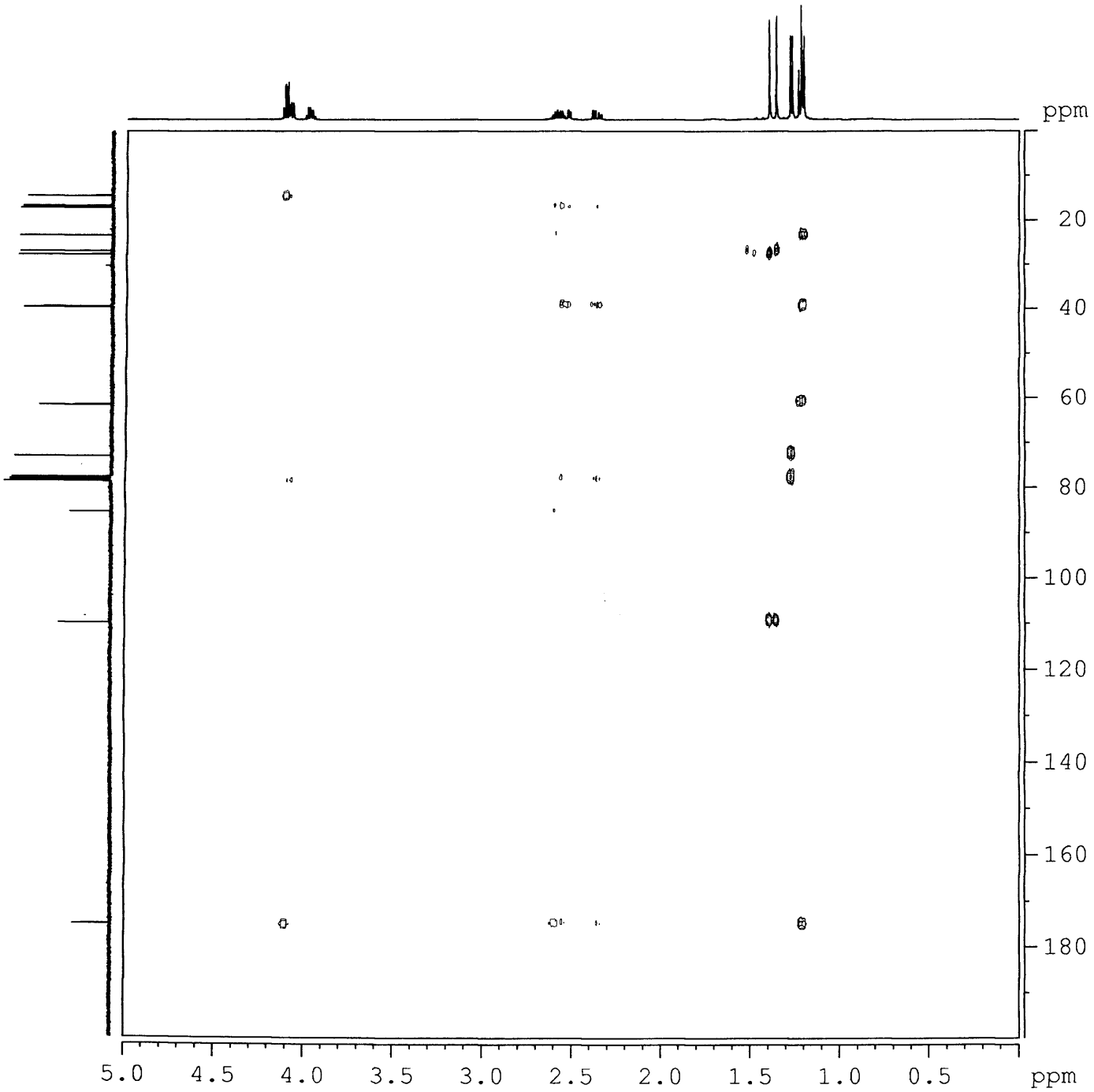


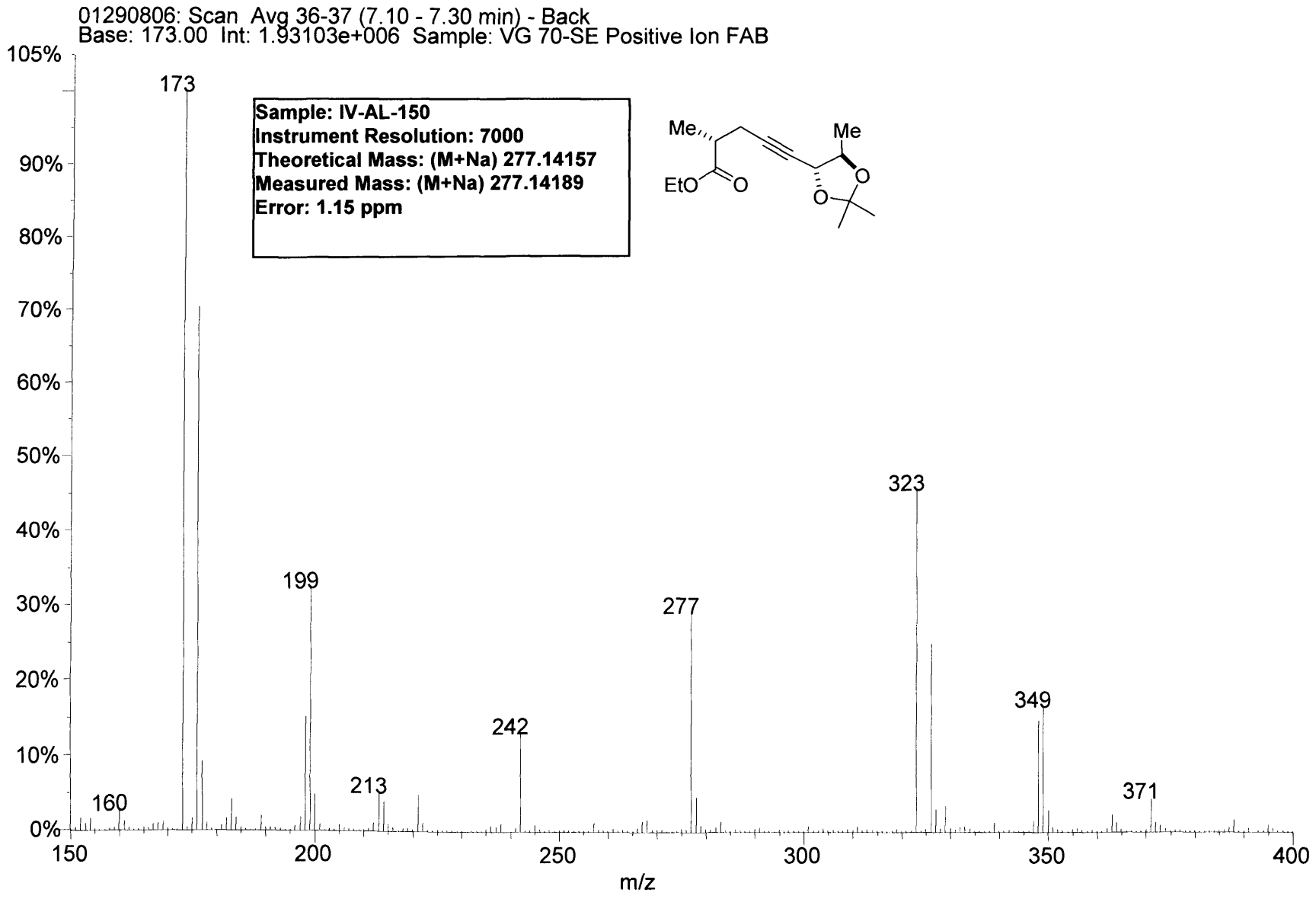
IV-AL-150
HMQC
CDCl3 - 298K

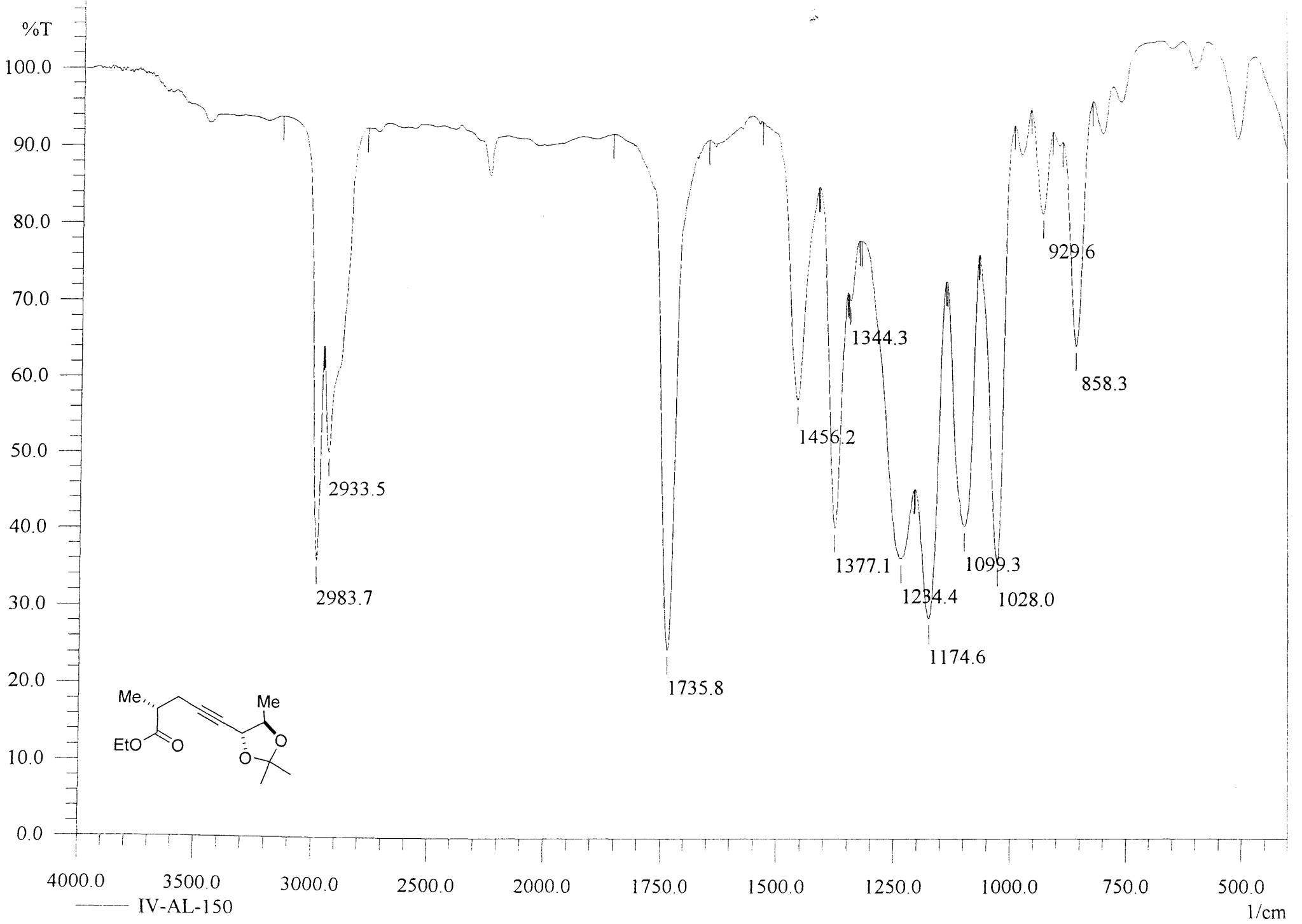


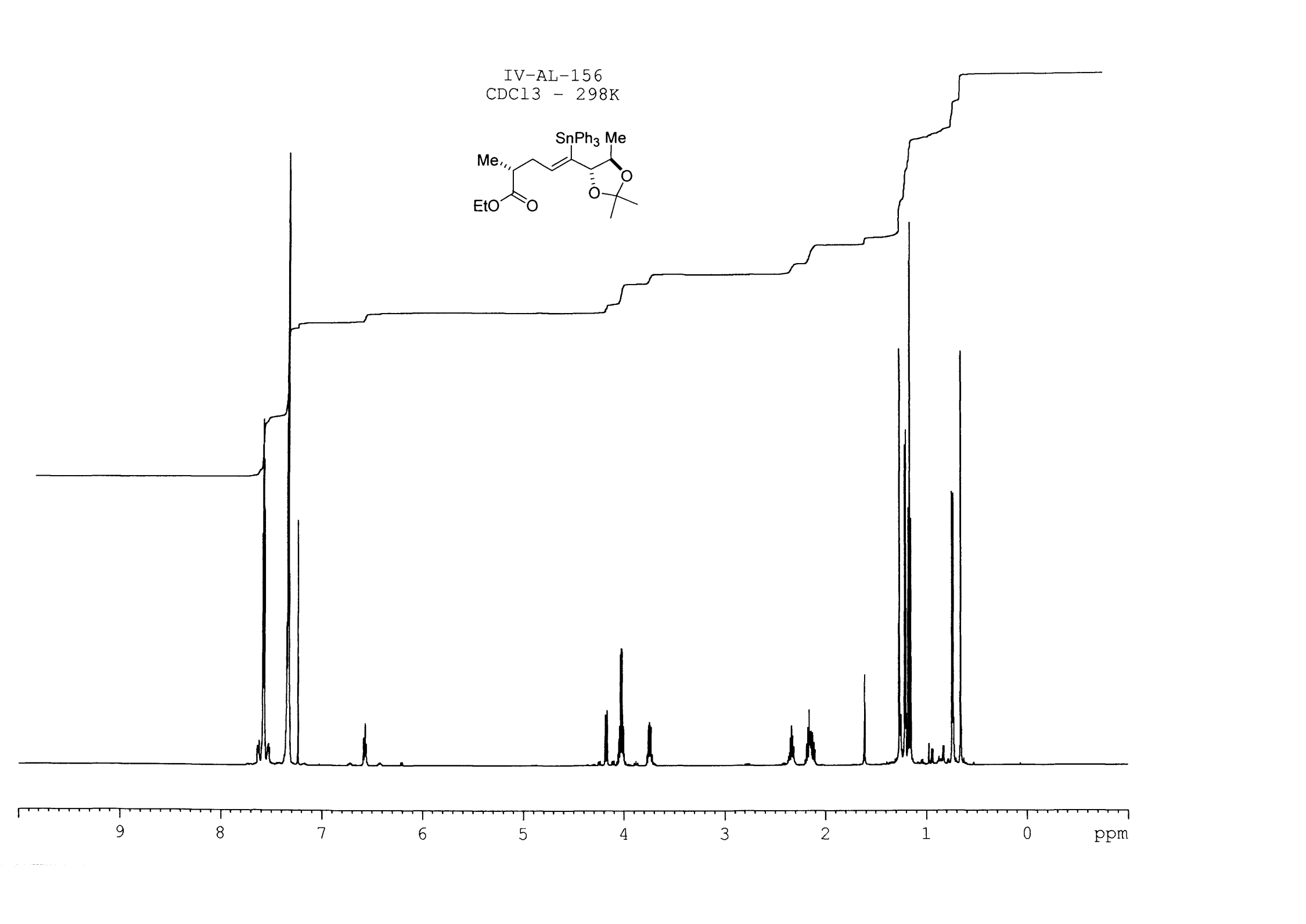
IV-AL-150
HMBC
CDCl3 - 298K



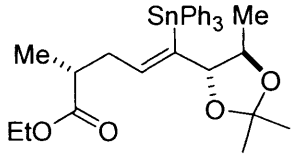


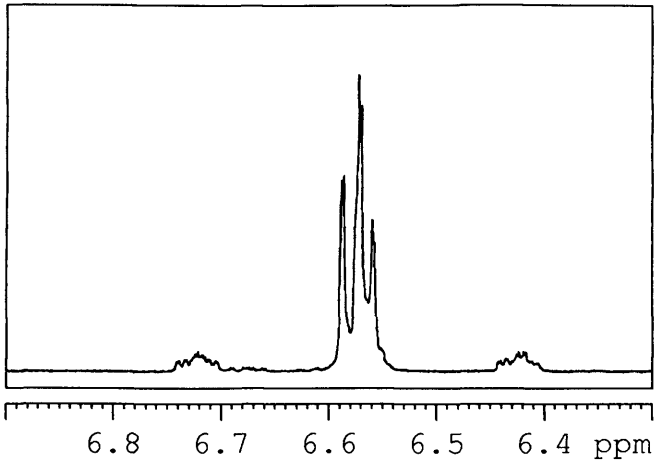

01290806: Scan Avg 36-37 (7.10 - 7.30 min) - Back
Base: 173.00 Int: 1.93103e+006 Sample: VG 70-SE Positive Ion FAB
Sample: IV-AL-150
Instrument Resolution: 7000
Theoretical Mass: (M+Na) 277.14157
Measured Mass: (M+Na) 277.14189
Error: 1.15 ppm
Me
Me
EtO
O
O
O
105%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
173
199
160
213
242
277
323
349
371
150
200
250
300
350
400
m/z


%T
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
2983.7
2933.5
1735.8
1456.2
1377.1
1344.3
1234.4
1174.6
1099.3
1028.0
929.6
858.3
Me
Me
EtO
O
O
O
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
IV-AL-150

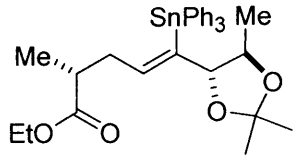

IV-AL-156
CDCl3 - 298K
SnPh3 Me
Me
EtO
O
O
O
9
8
7
6
5
4
3
2
1
0
ppm

IV-AL-156
CDCl3 - 298K

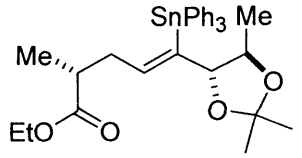


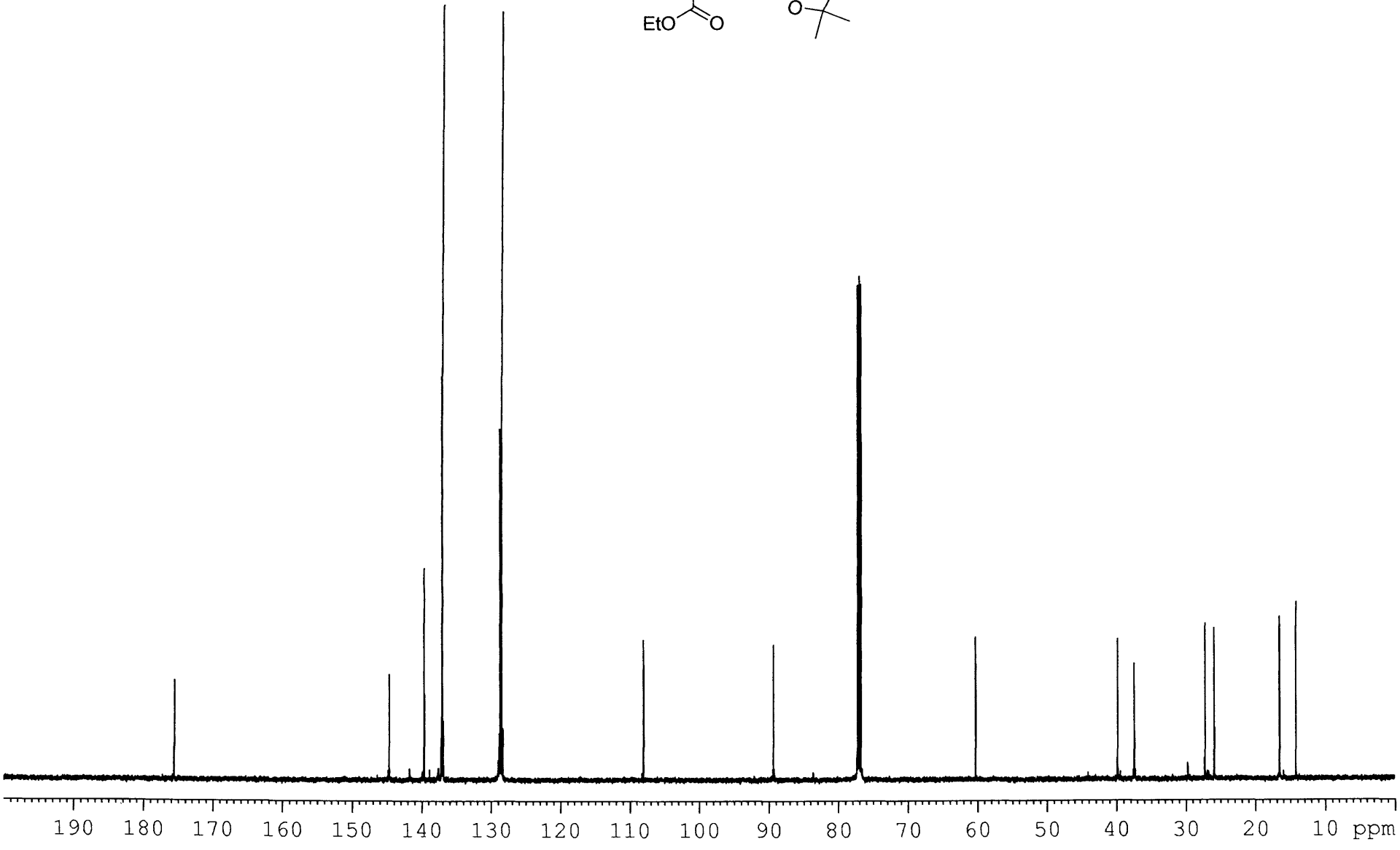


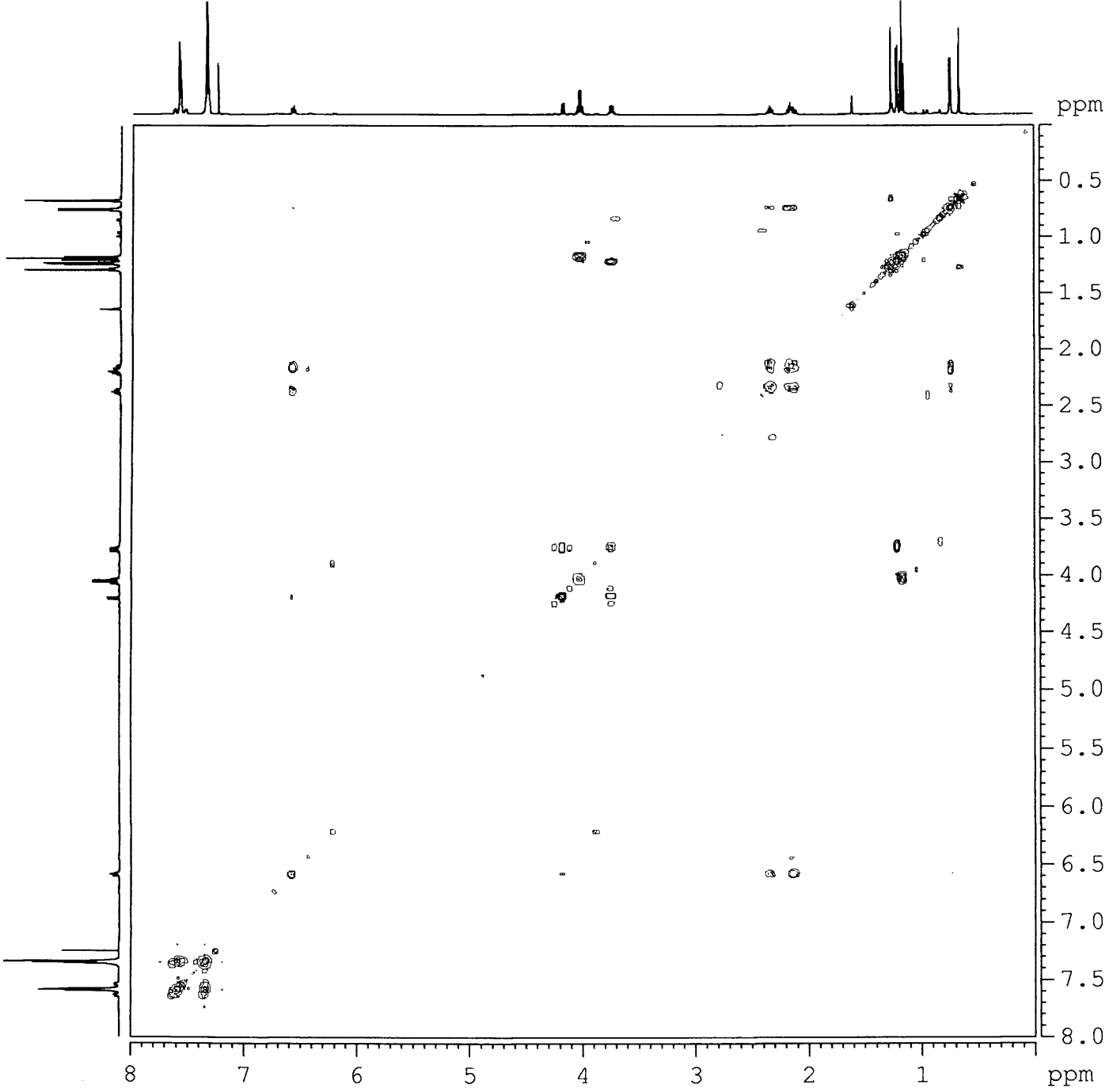
IV-AL-156
DEPT
CDCl3 - 298K



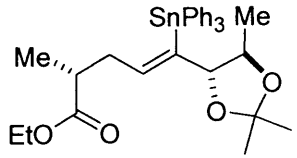
IV-AL-156
13C
CDCl3 - 298K

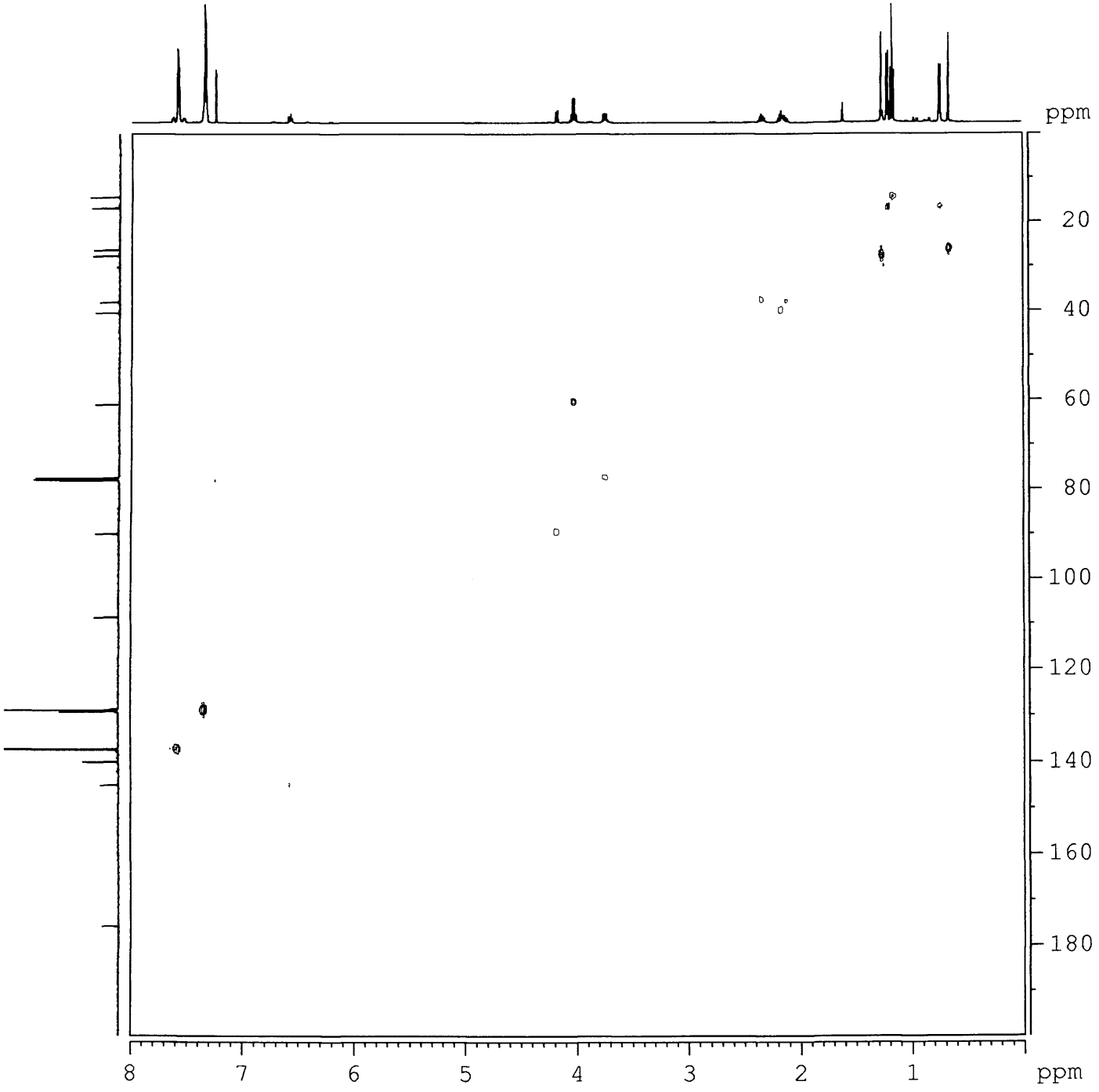




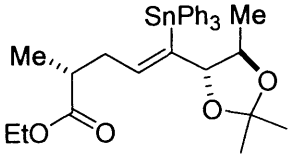


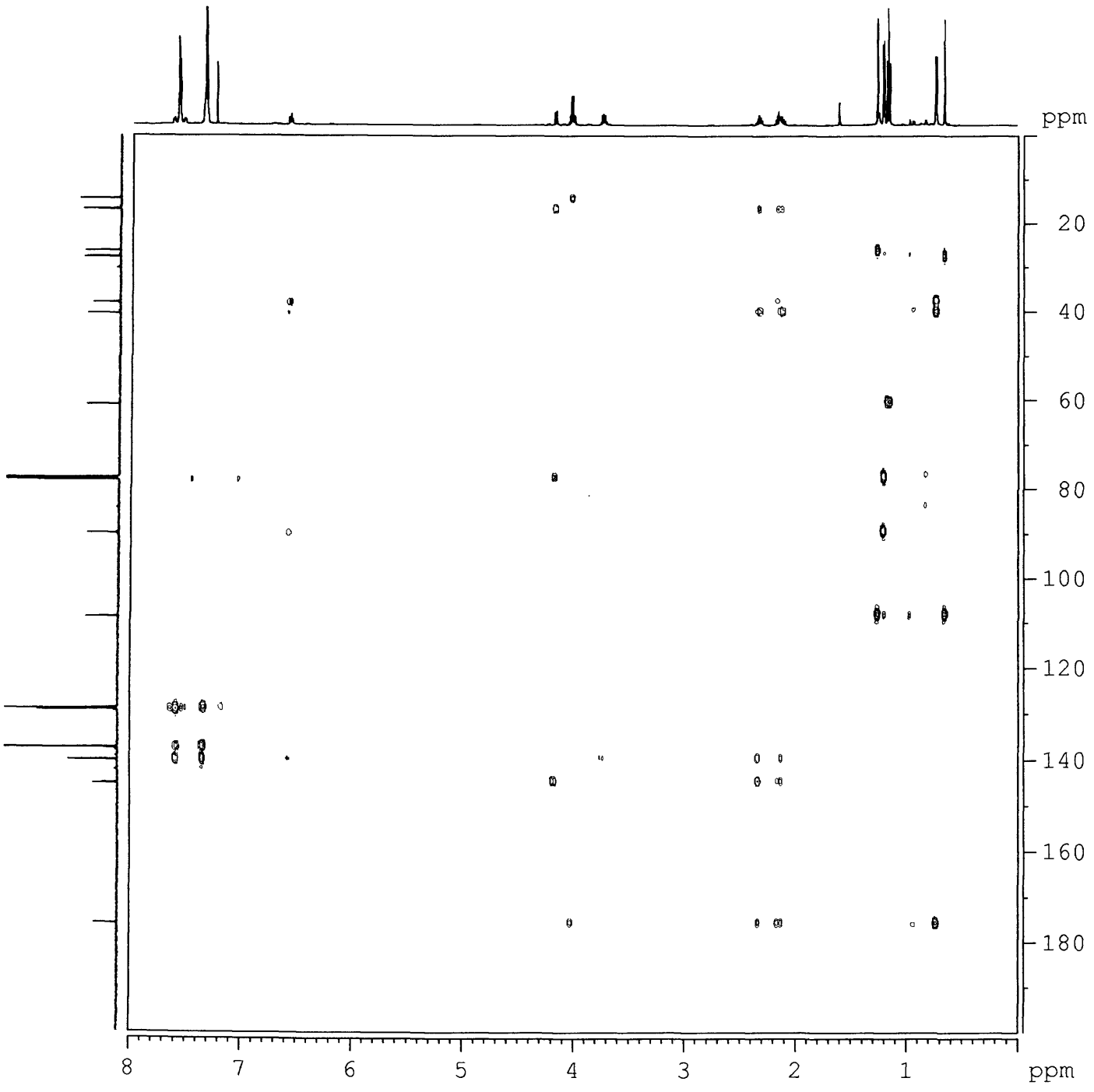
IV-AL-156
COSY
CDCl3 - 298K



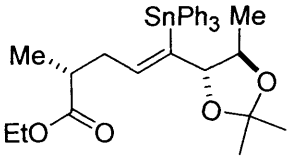


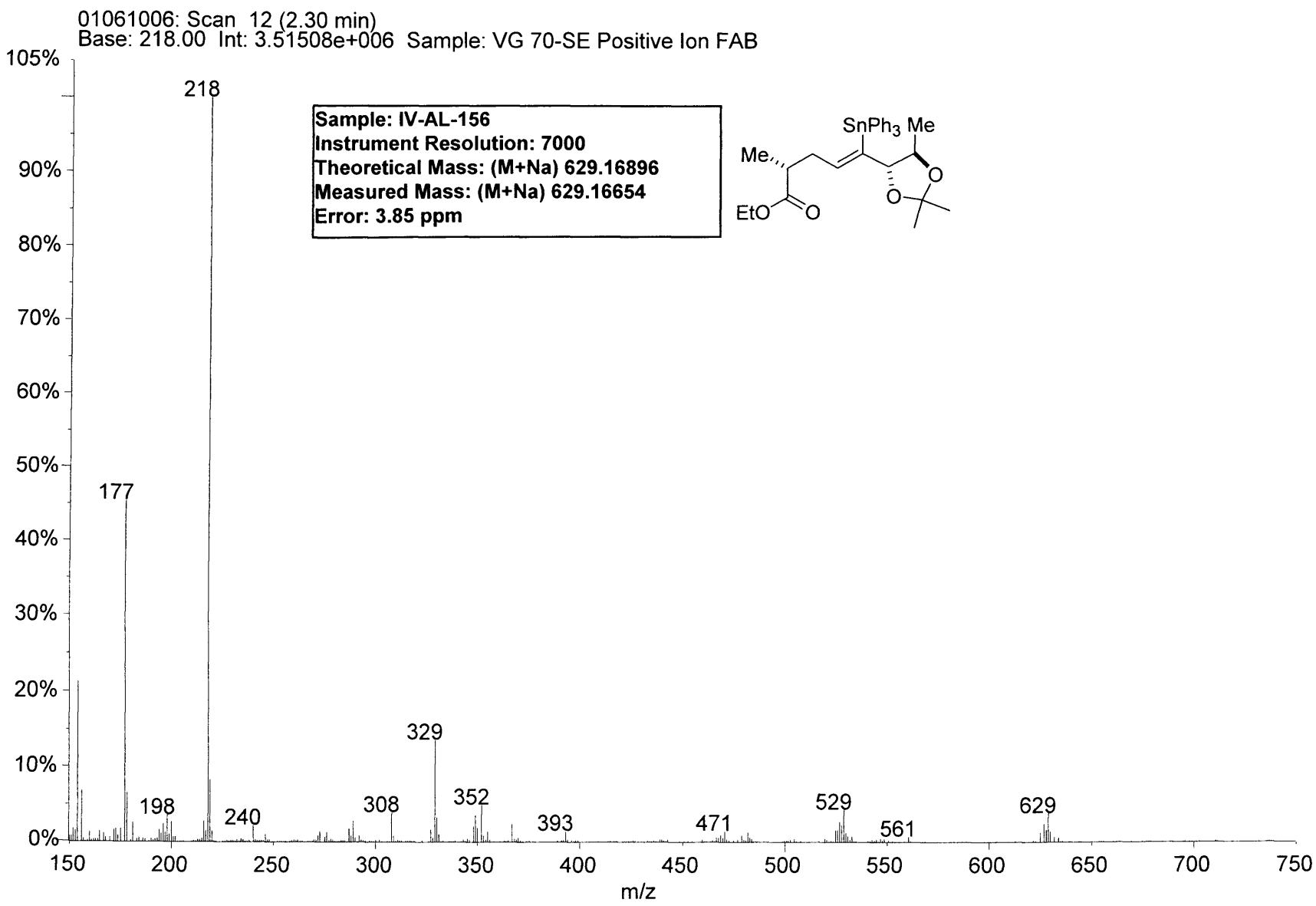
IV-AL-156
HMQC
CDCl3 - 298K

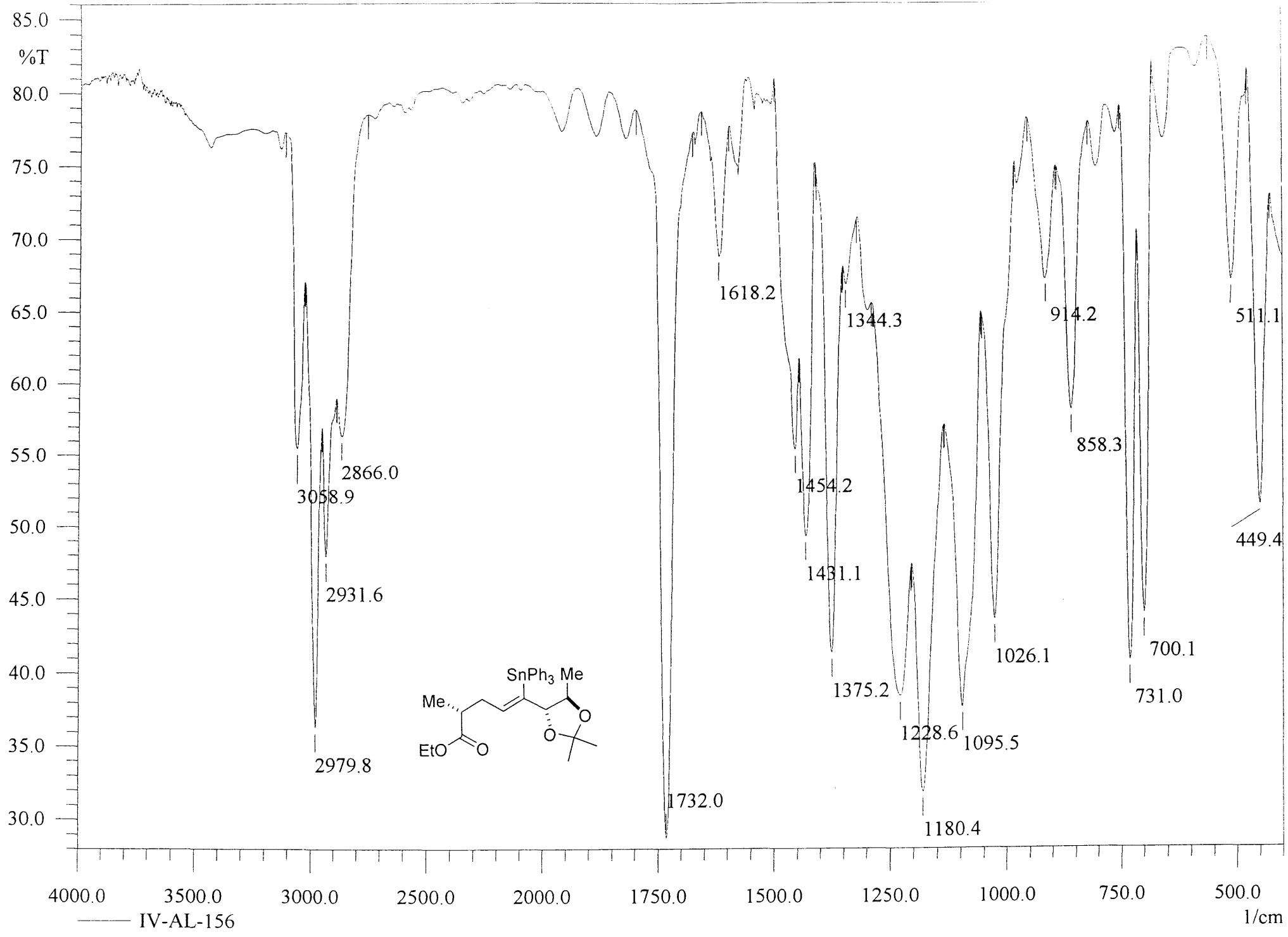




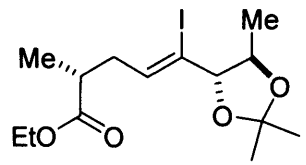
IV-AL-156
HMBC
CDCl3 - 298K



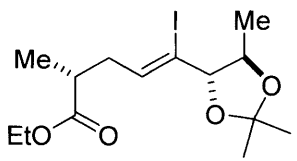

01061006: Scan 12 (2.30 min)
Base: 218.00 Int: 3.51508e+006 Sample: VG 70-SE Positive Ion FAB
Sample: IV-AL-156
Instrument Resolution: 7000
Theoretical Mass: (M+Na) 629.16896
Measured Mass: (M+Na) 629.16654
Error: 3.85 ppm
SnPh3 Me
Me
EtO
O
O
O
105%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
218
177
198
240
308
329
352
393
471
529
561
629
150
200
250
300
350
400
450
500
550
600
650
700
750
m/z

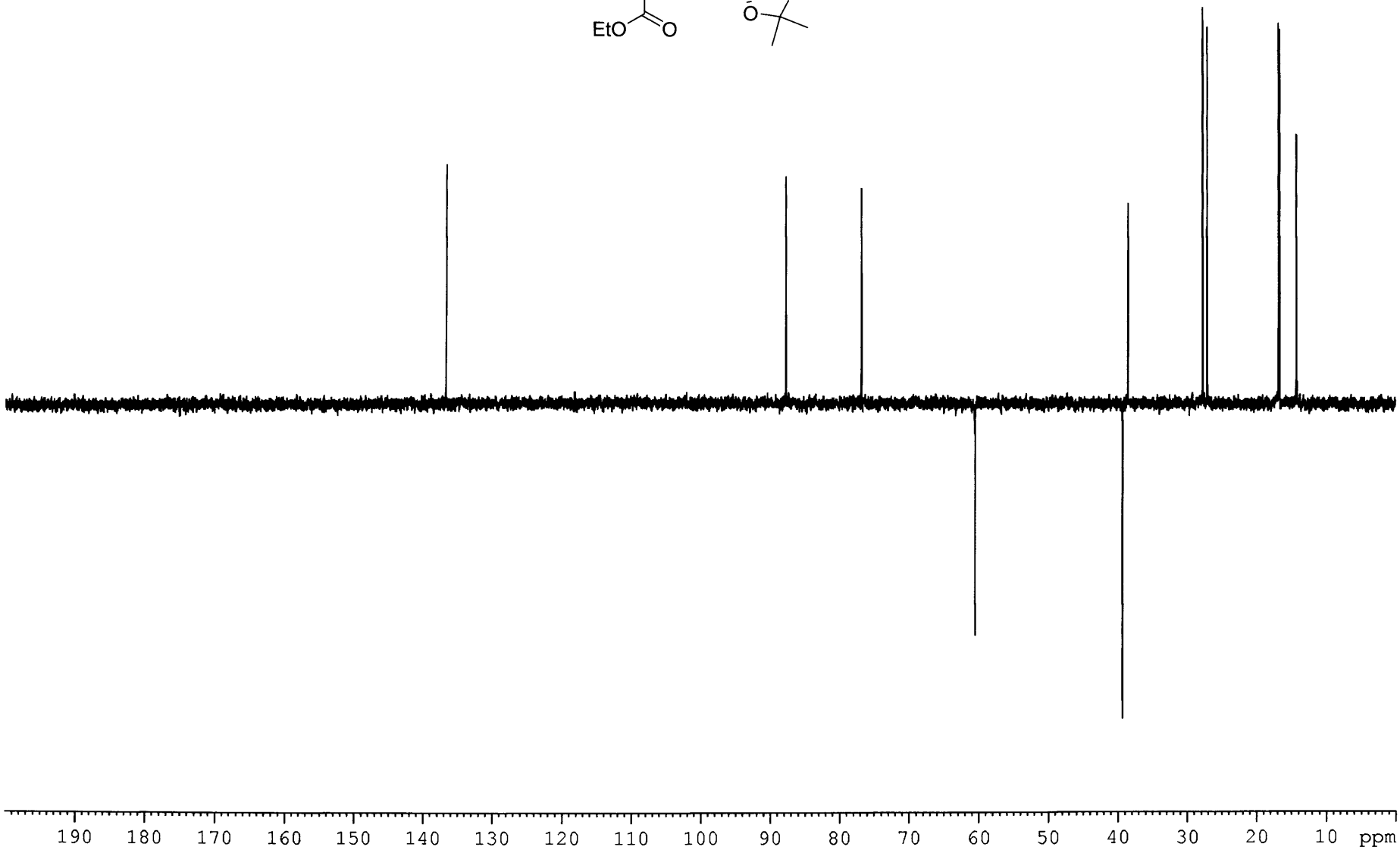

85.0
%T
80.0
75.0
70.0
65.0
60.0
55.0
50.0
45.0
40.0
35.0
30.0
3058.9
2866.0
2931.6
2979.8
1732.0
1618.2
1454.2
1431.1
1375.2
1344.3
1228.6
1180.4
1095.5
1026.1
914.2
858.3
731.0
700.1
511.1
449.4
SnPh3 Me
Me
EtO
O
O
O
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
IV-AL-156

IV-AL-160
CDCl3 - 298K

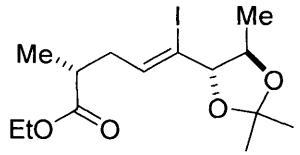


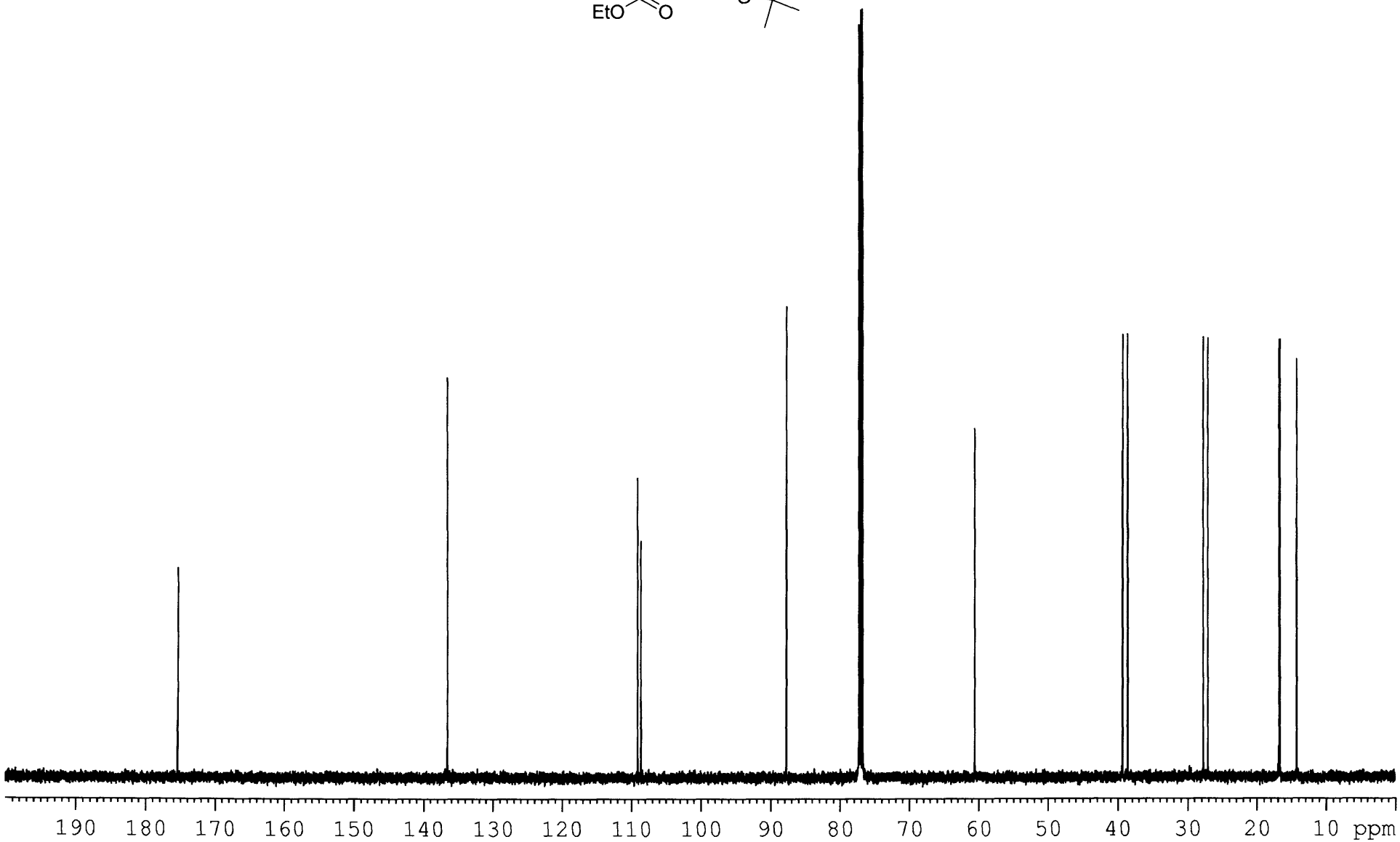
IV-AL-160
DEPT
CDCL3 - 298K

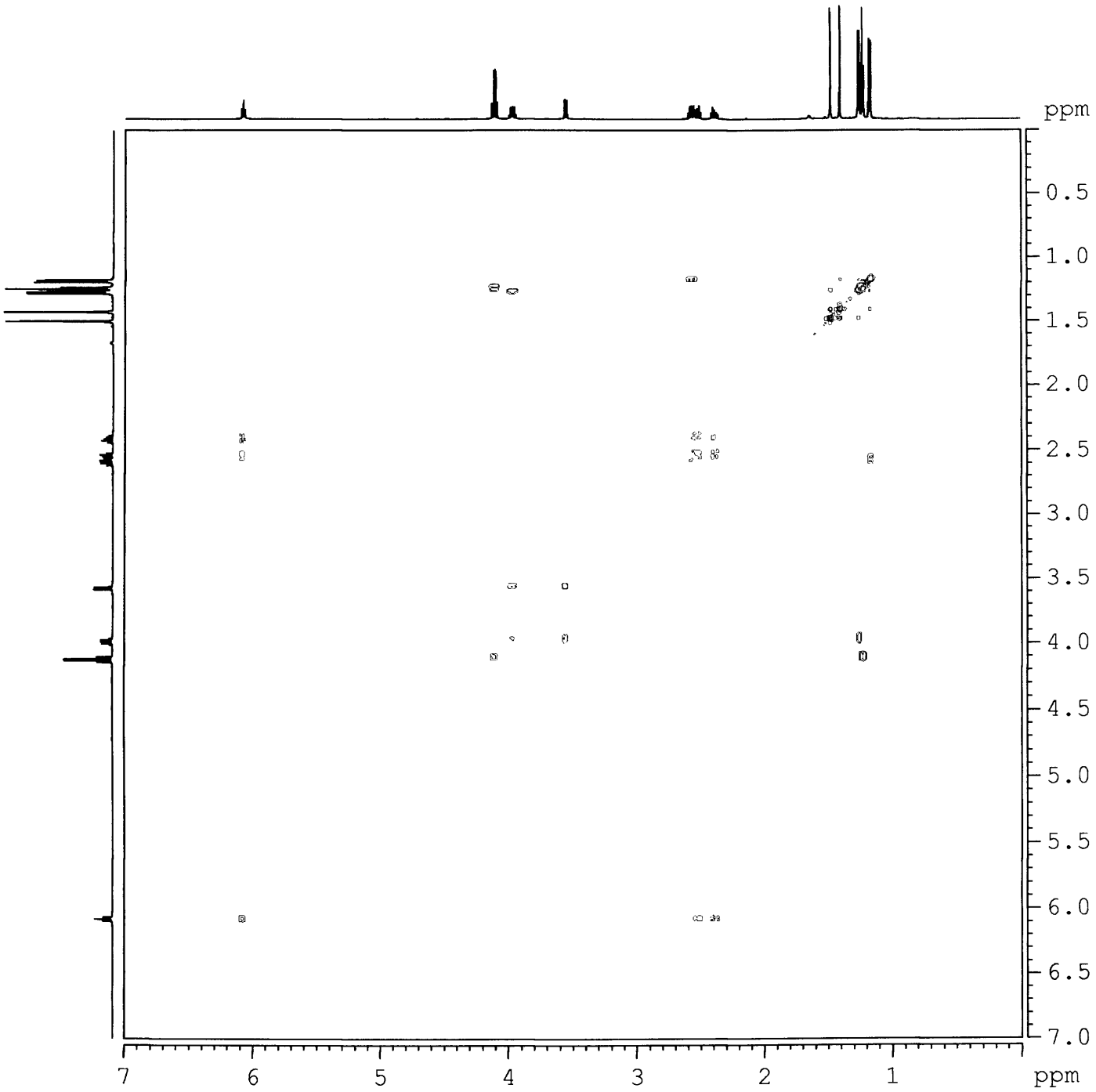




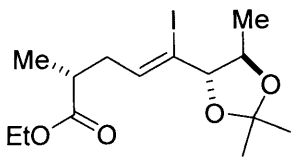
IV-AL-160
13C
CDCl3 - 298K



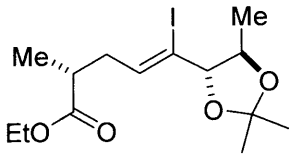


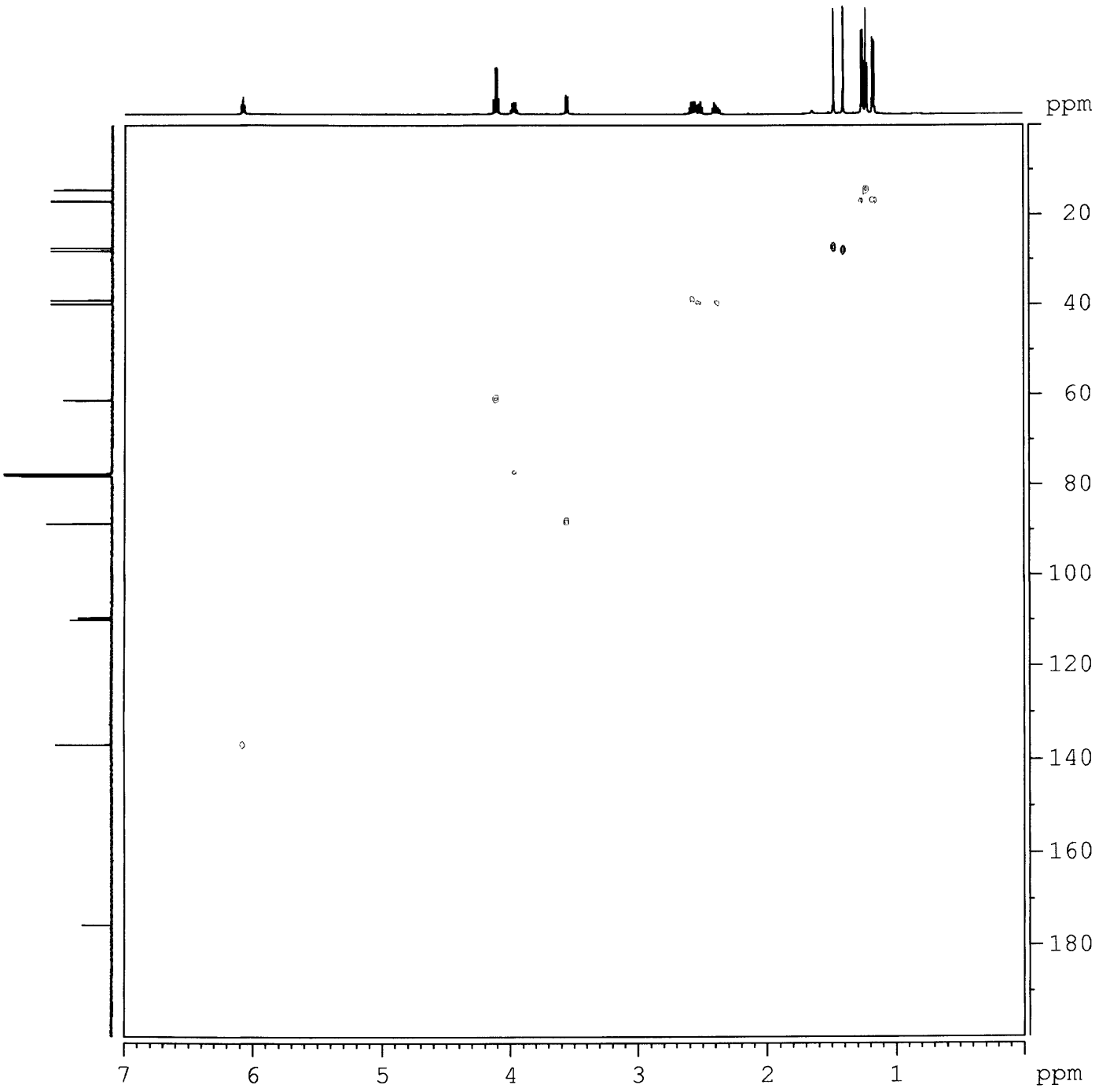


IV-AL-160
COSY
CDCl3 - 298K

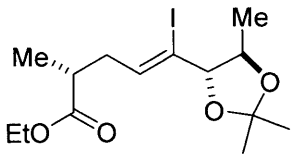


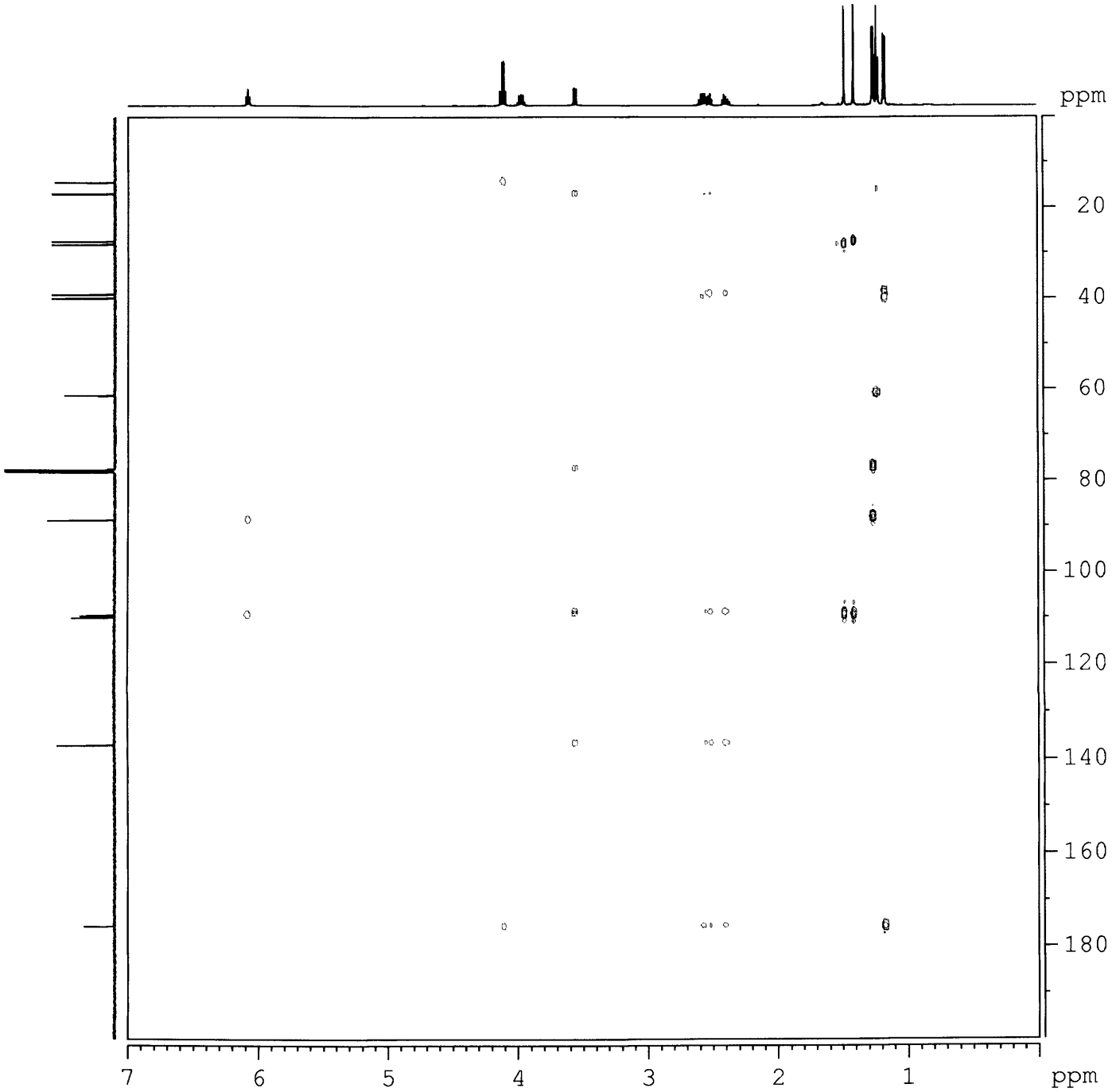
IV-AL-160
HMQC
CDCl3 - 298K

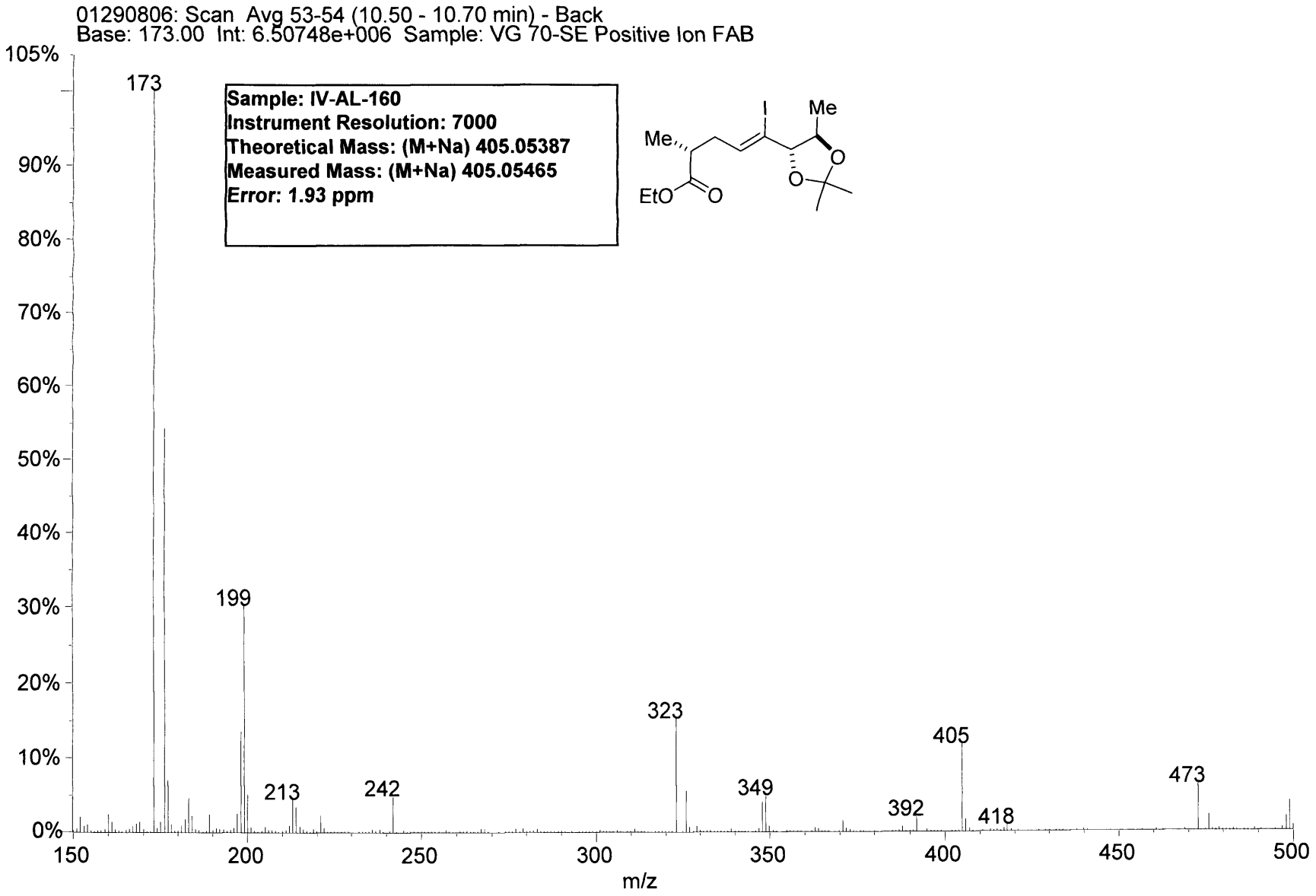


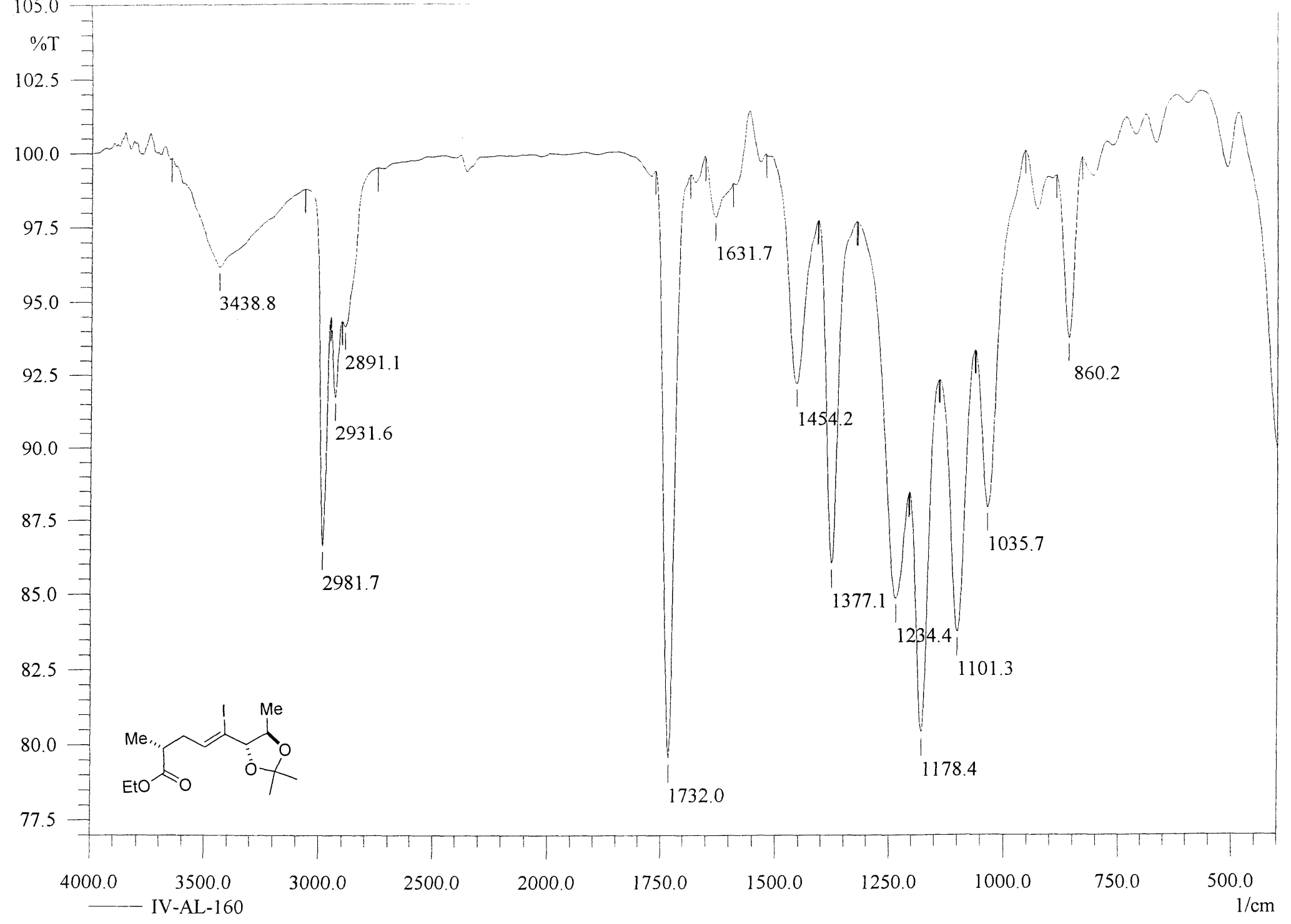


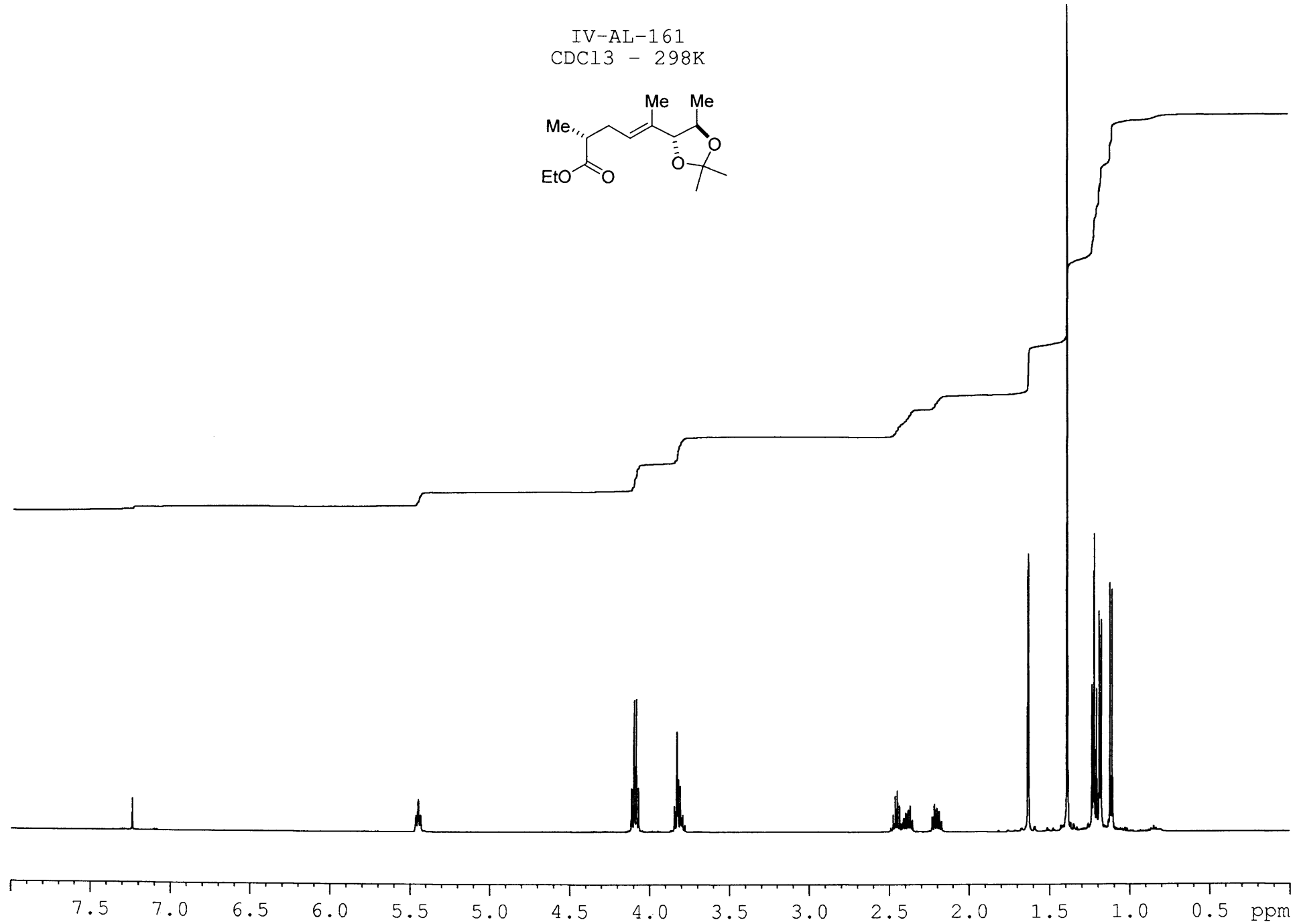
IV-AL-160
HMBC
CDCL3 - 298K



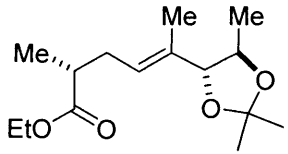


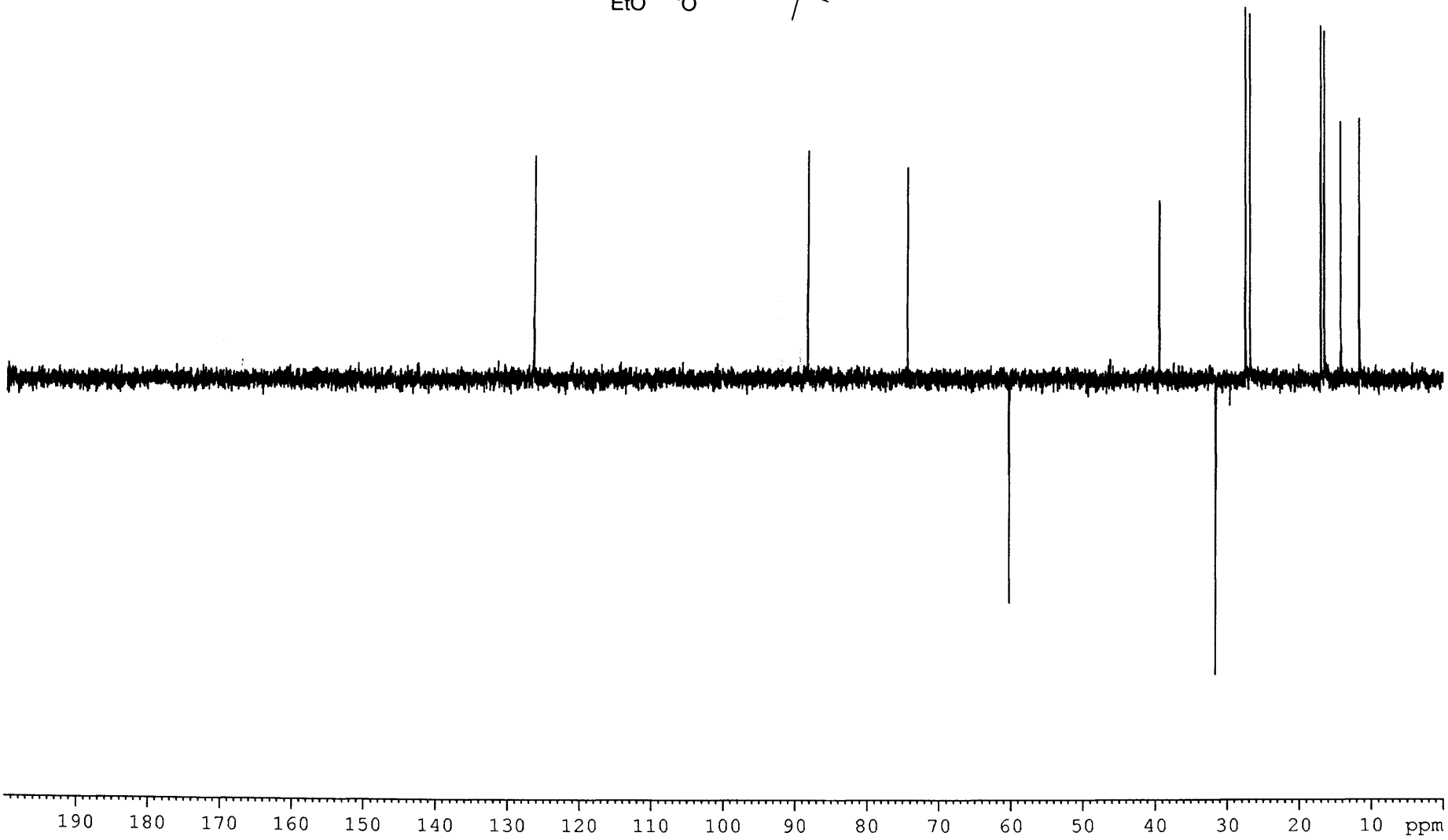

01290806: Scan Avg 53-54 (10.50 - 10.70 min) - Back
Base: 173.00 Int: 6.50748e+006 Sample: VG 70-SE Positive Ion FAB
Sample: IV-AL-160
Instrument Resolution: 7000
Theoretical Mass: (M+Na) 405.05387
Measured Mass: (M+Na) 405.05465
Error: 1.93 ppm
Me
I
Me
O
O
EtO
O
105%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
173
199
213
242
323
349
392
405
418
473
150
200
250
300
350
400
450
500
m/z


105.0
%T
102.5
100.0
97.5
95.0
92.5
90.0
87.5
85.0
82.5
80.0
77.5
3438.8
2891.1
2931.6
2981.7
1732.0
1631.7
1454.2
1377.1
1234.4
1178.4
1101.3
1035.7
860.2
Me
I
Me
O
O
EtO
O
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
IV-AL-160

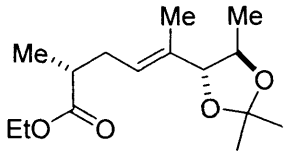

IV-AL-161
CDCl3 - 298K
Me
Me
Me
EtO
O
O
O
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

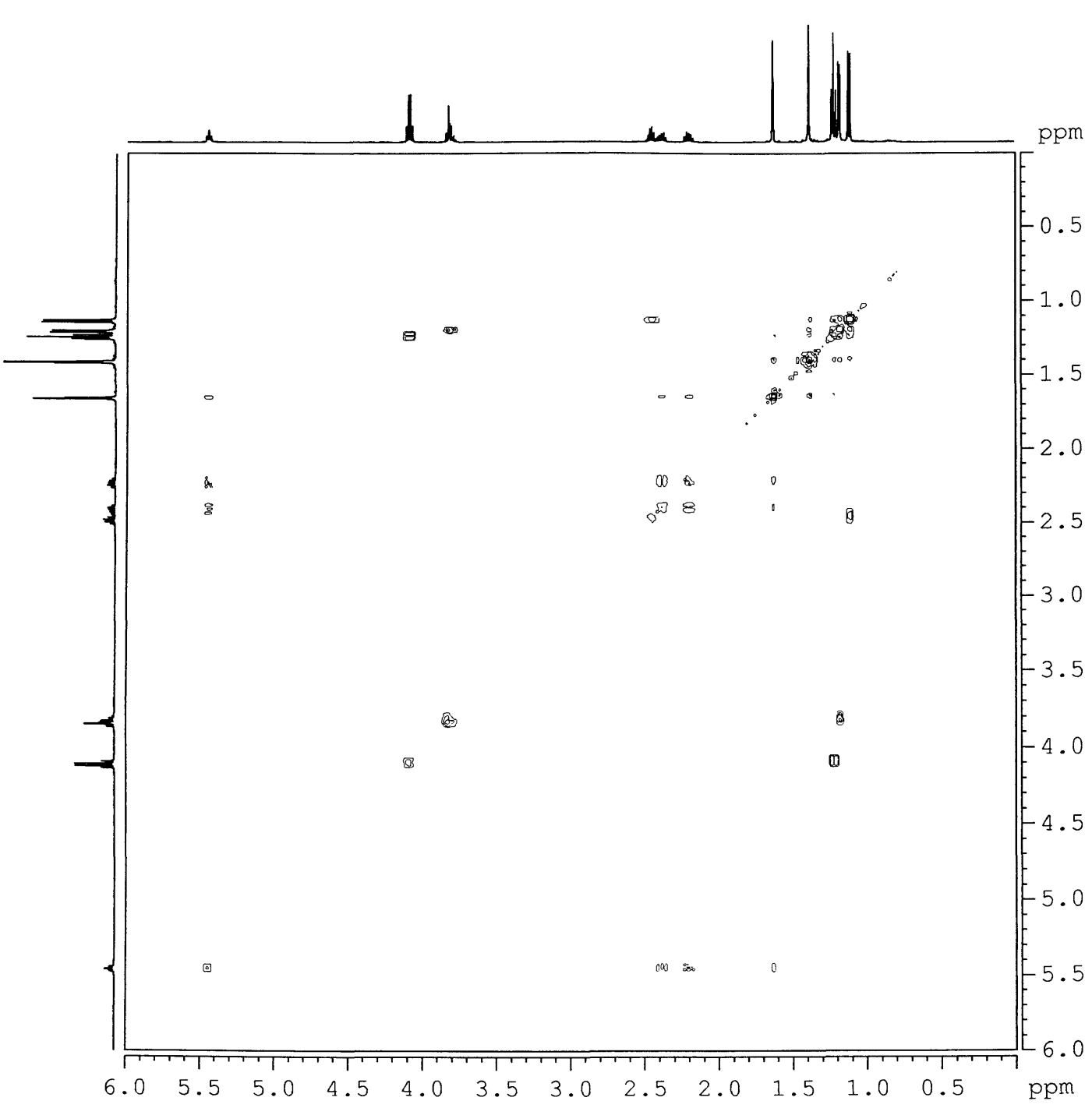
IV-AL-161
DEPT
CDCl3 - 298K



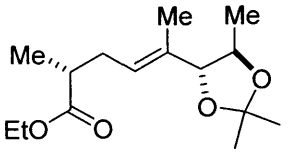


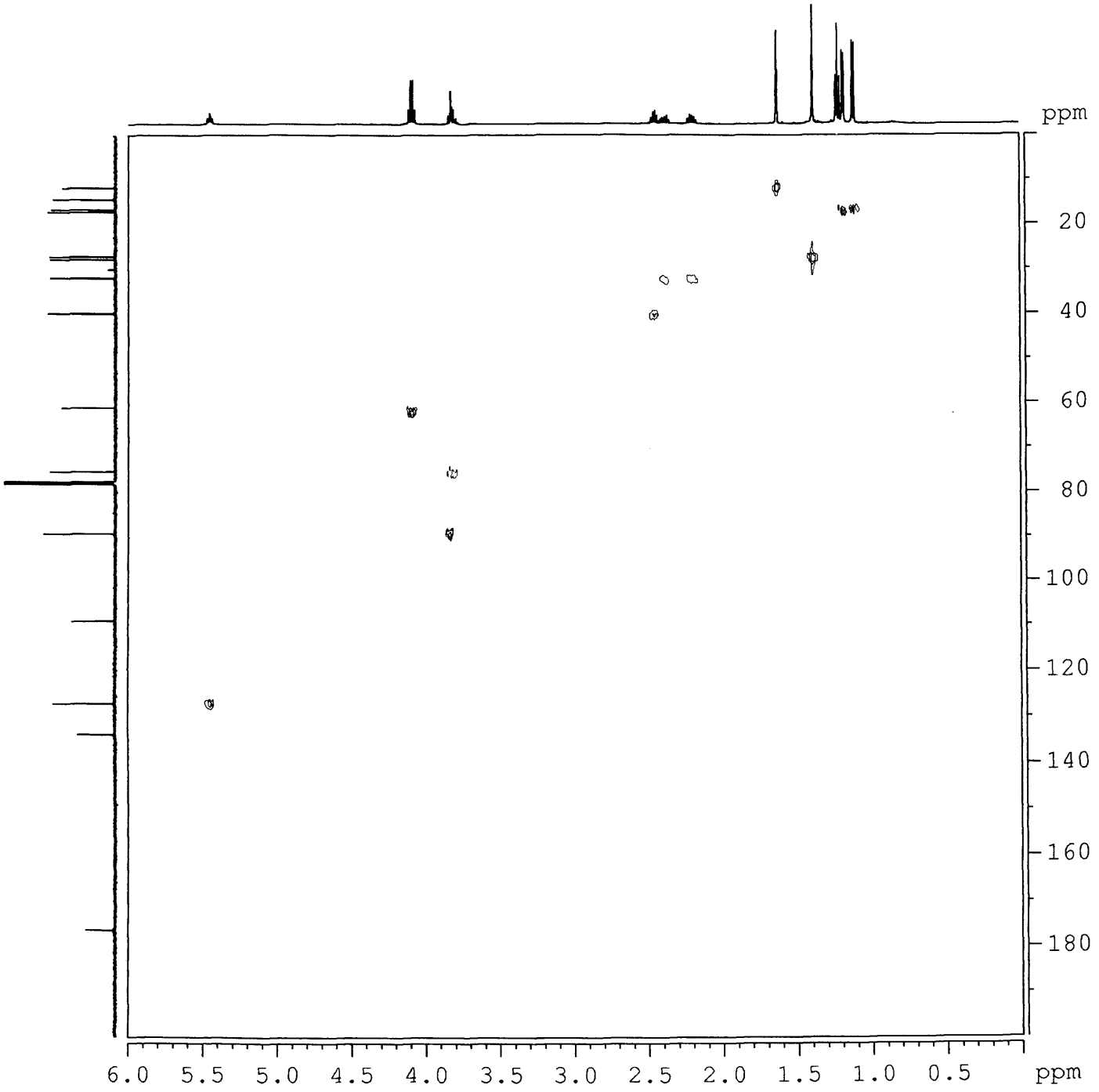
IV-AL-161
13C
CDCl3 - 298K



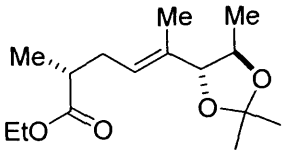


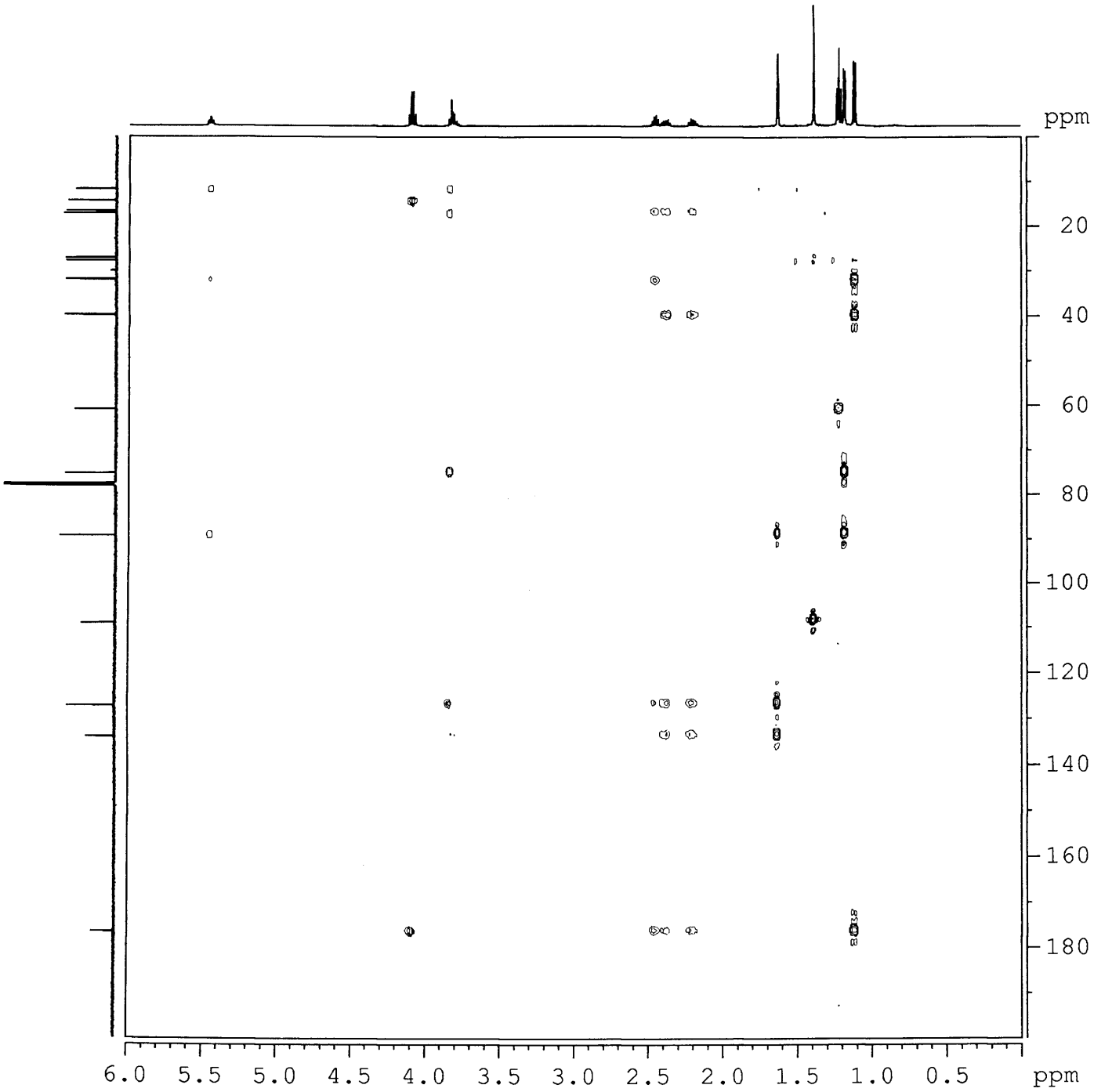
IV-AL-161
COSY
CDCl3 - 298K



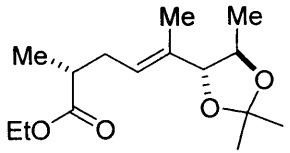


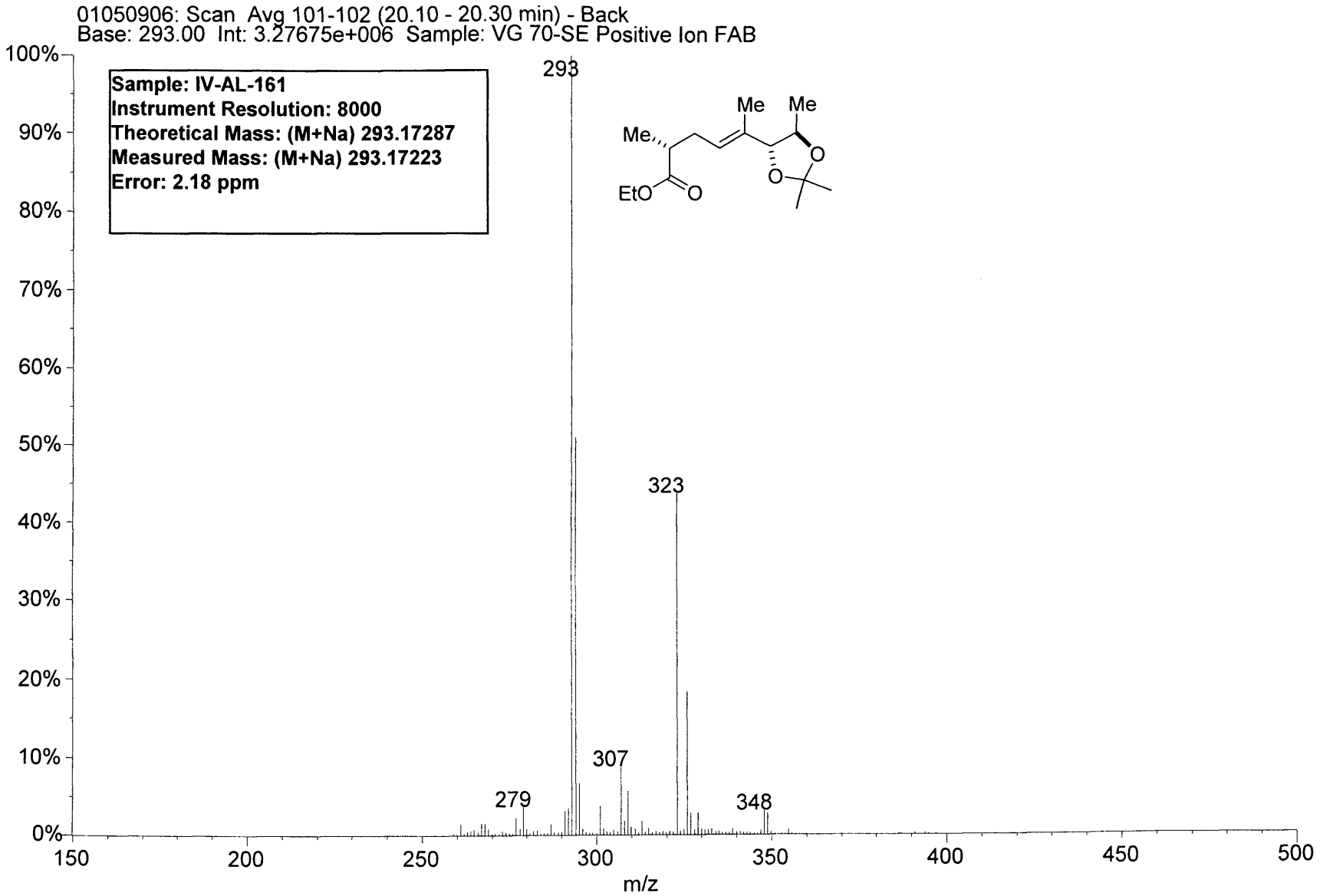
IV-AL-161
HMQC
CDCl3 - 298K

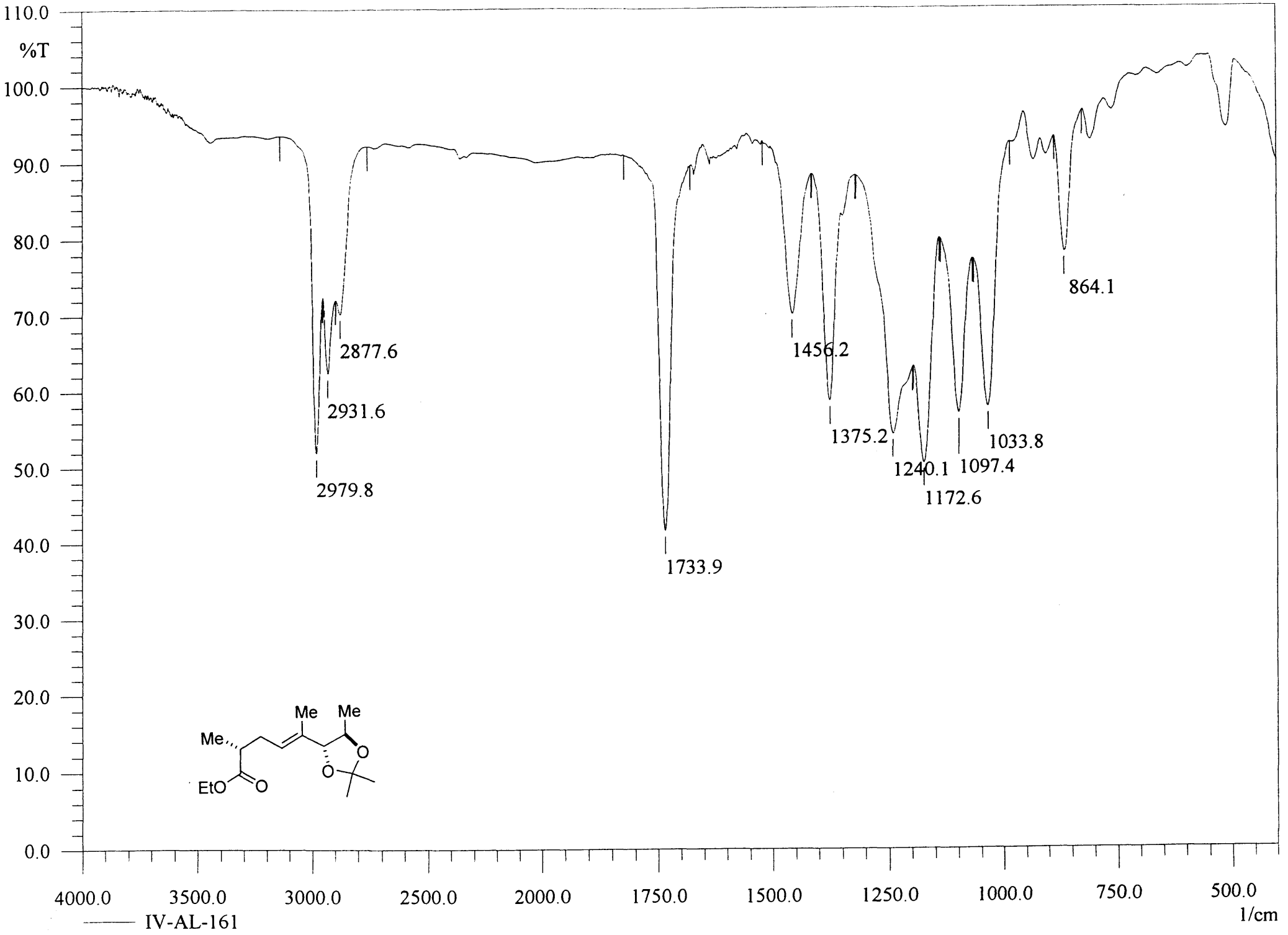




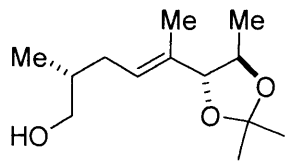
IV-AL-161
HMBC
CDCl3 - 298K



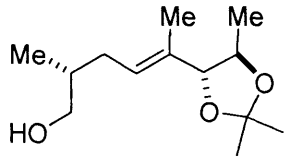

01050906: Scan Avg 101-102 (20.10 - 20.30 min) - Back
Base: 293.00 Int: 3.27675e+006 Sample: VG 70-SE Positive Ion FAB
Sample: IV-AL-161
Instrument Resolution: 8000
Theoretical Mass: (M+Na) 293.17287
Measured Mass: (M+Na) 293.17223
Error: 2.18 ppm
293
323
307
279
348
Me
Me
Me
EtO
O
O
O
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
150
200
250
300
350
400
450
500
m/z

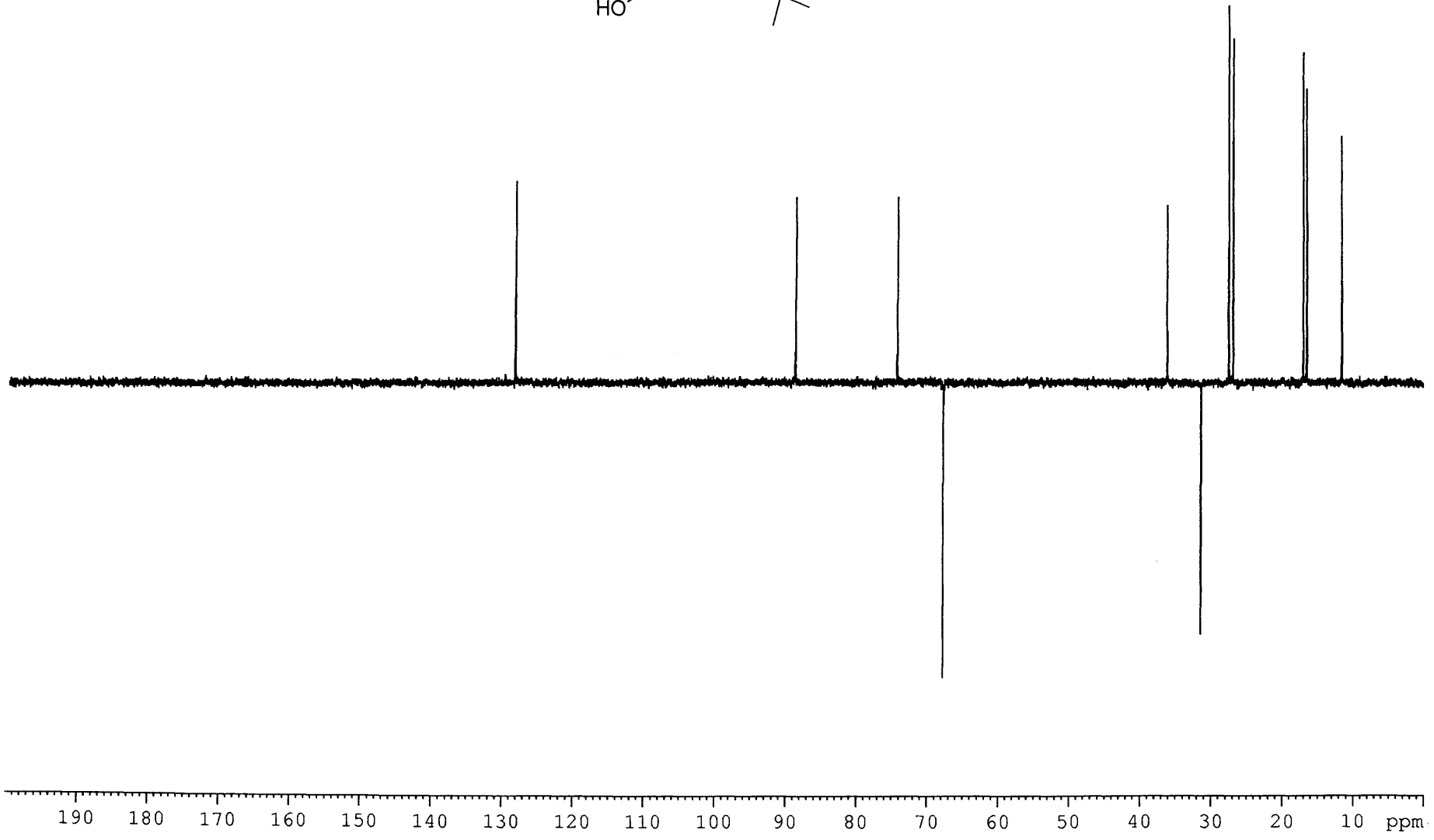

110.0
%T
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
2877.6
2931.6
2979.8
1733.9
1456.2
1375.2
1240.1
1172.6
1097.4
1033.8
864.1
Me
Me
Me
EtO
O
O
O
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
IV-AL-161

IV-AL-168-2
CDCl3 - 298K

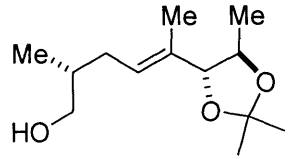


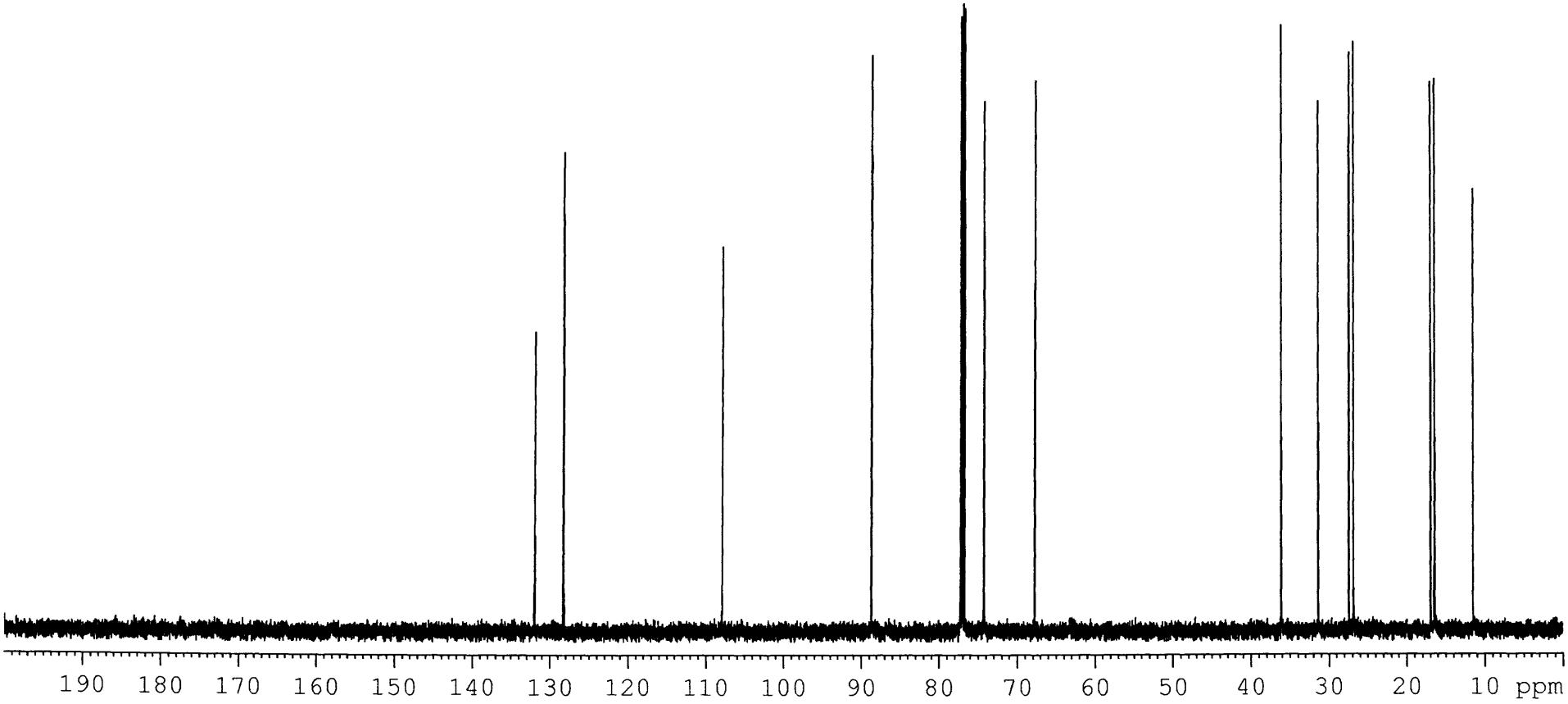
IV-AL-168-2
DEPT
CDCl3 - 298K

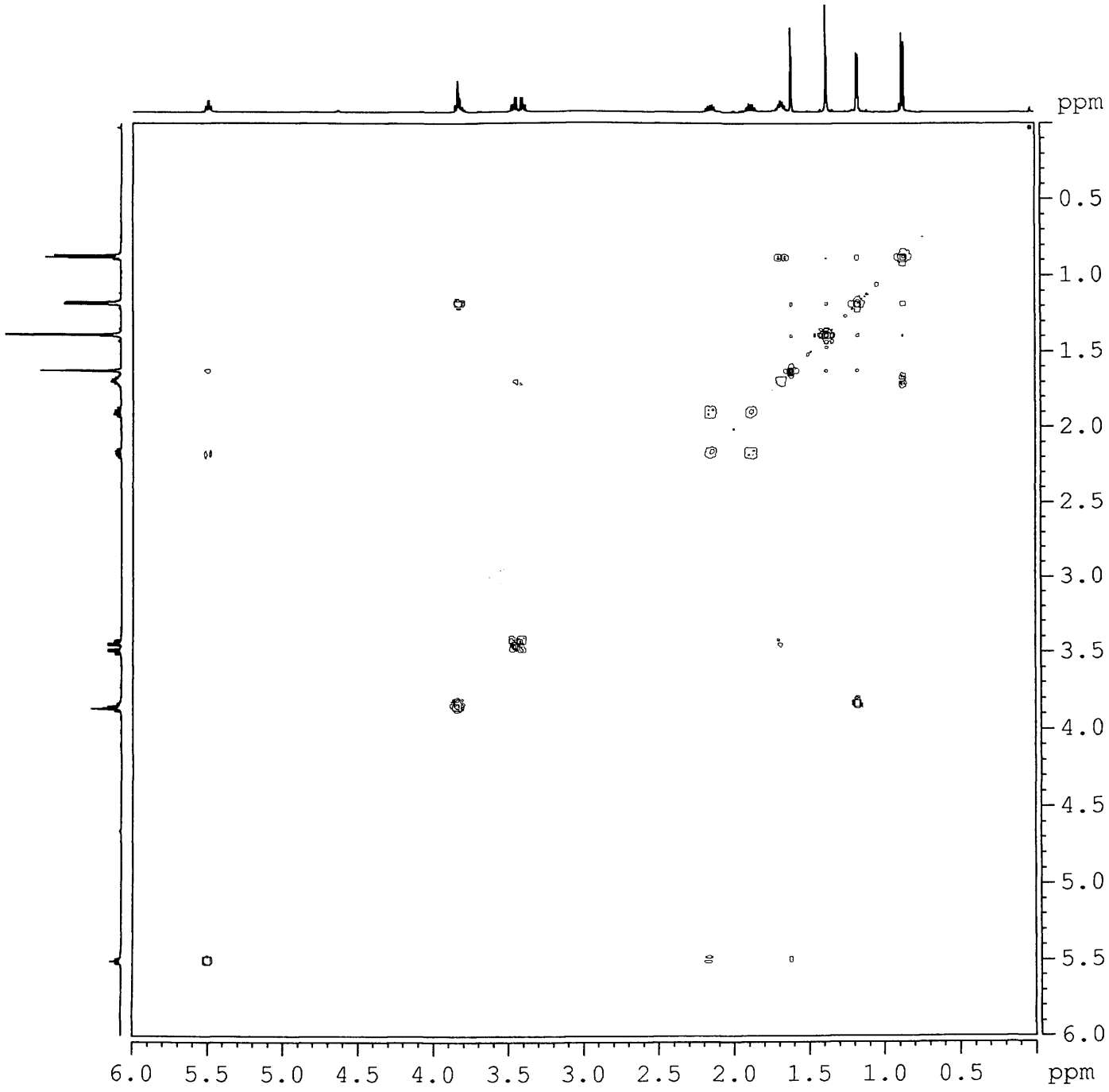




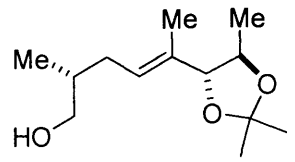
IV-AL-168-2
13C
CDCl3 - 298K



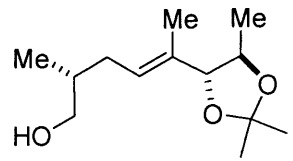


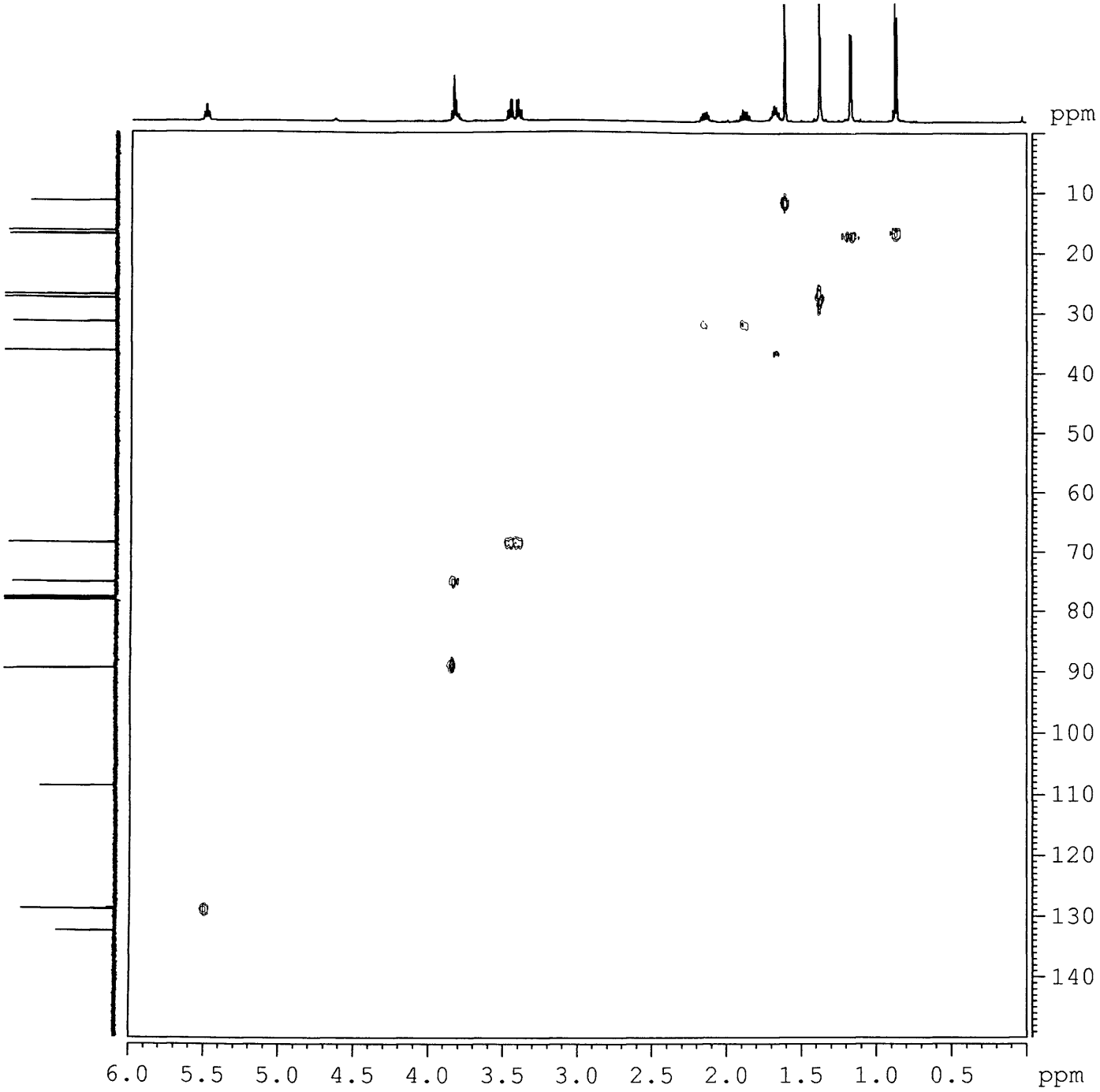


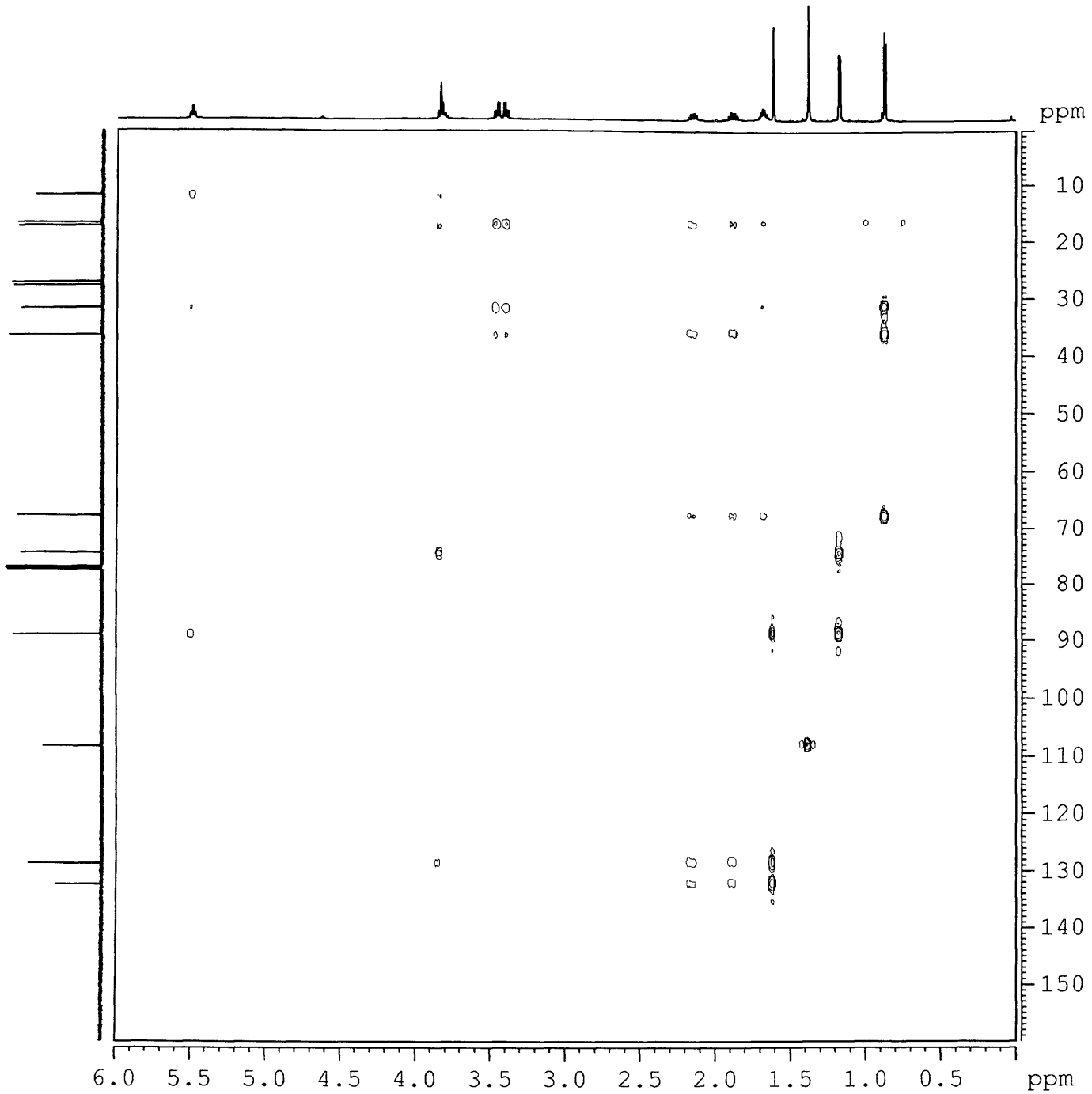
IV-AL-168-2
COSY
CDCl3 - 298K



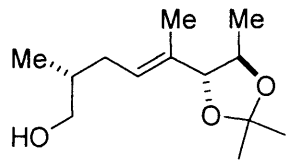
IV-AL-168-2
HMQC
CDCl3 - 298K

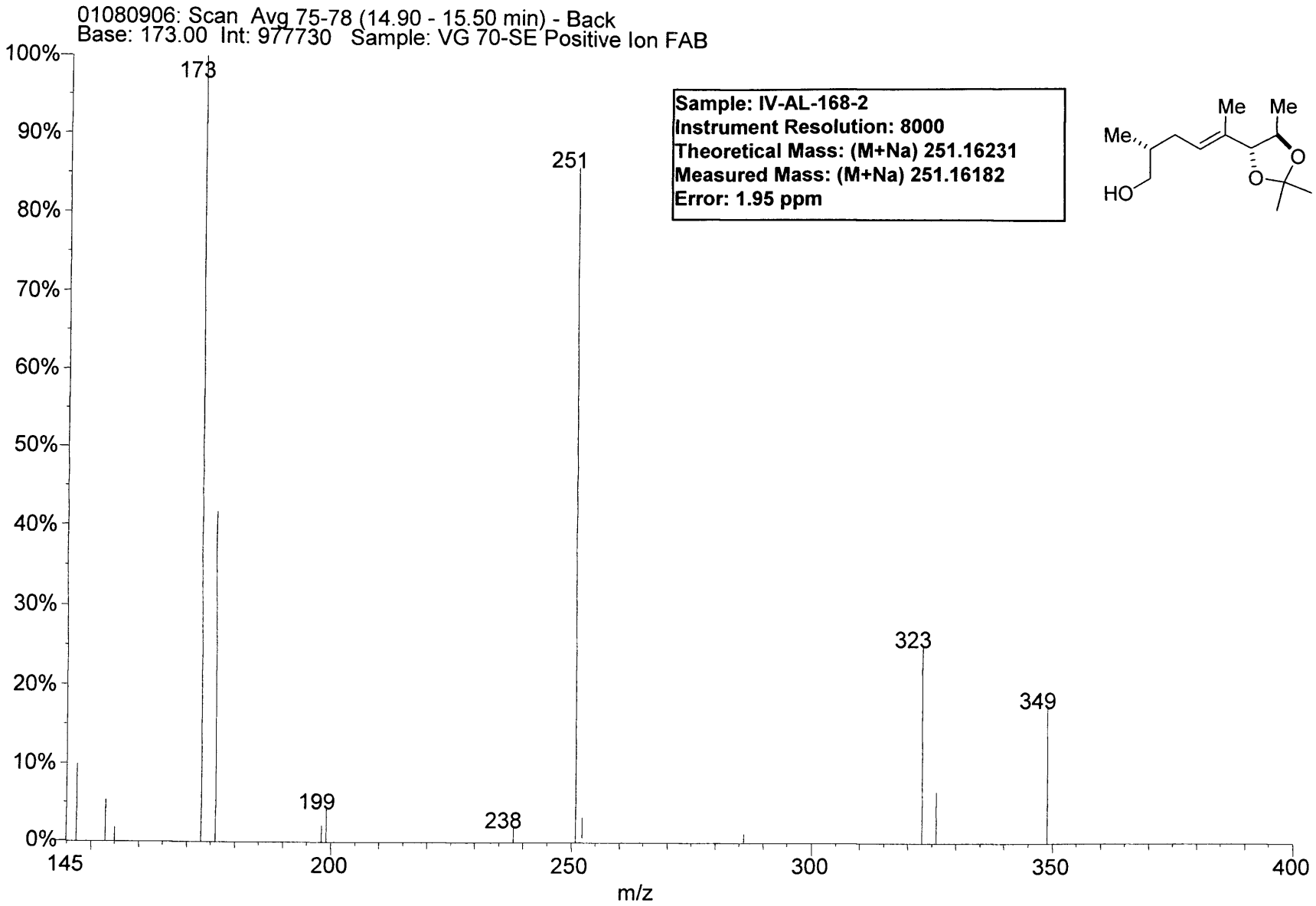


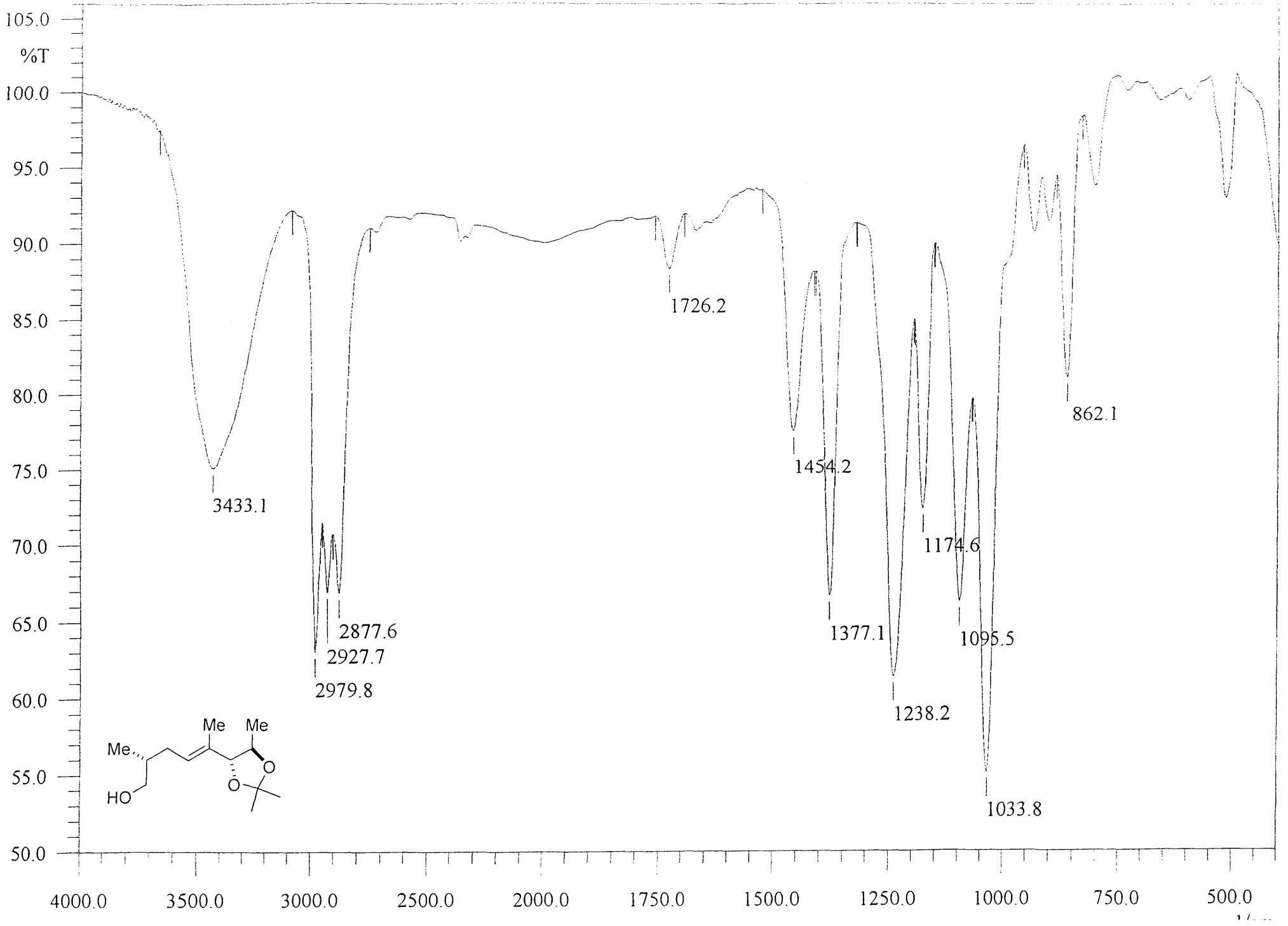




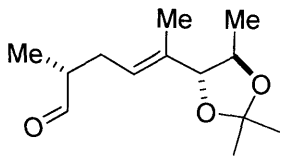
IV-AL-168-2
HMBC
CDCl3 - 298K



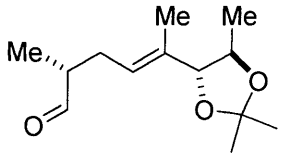

01080906: Scan Avg 75-78 (14.90 - 15.50 min) - Back
Base: 173.00 Int: 977730 Sample: VG 70-SE Positive Ion FAB
Sample: IV-AL-168-2
Instrument Resolution: 8000
Theoretical Mass: (M+Na) 251.16231
Measured Mass: (M+Na) 251.16182
Error: 1.95 ppm
Me
Me
Me
HO
O
O
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
173
251
323
349
199
238
145
200
250
300
350
400
m/z

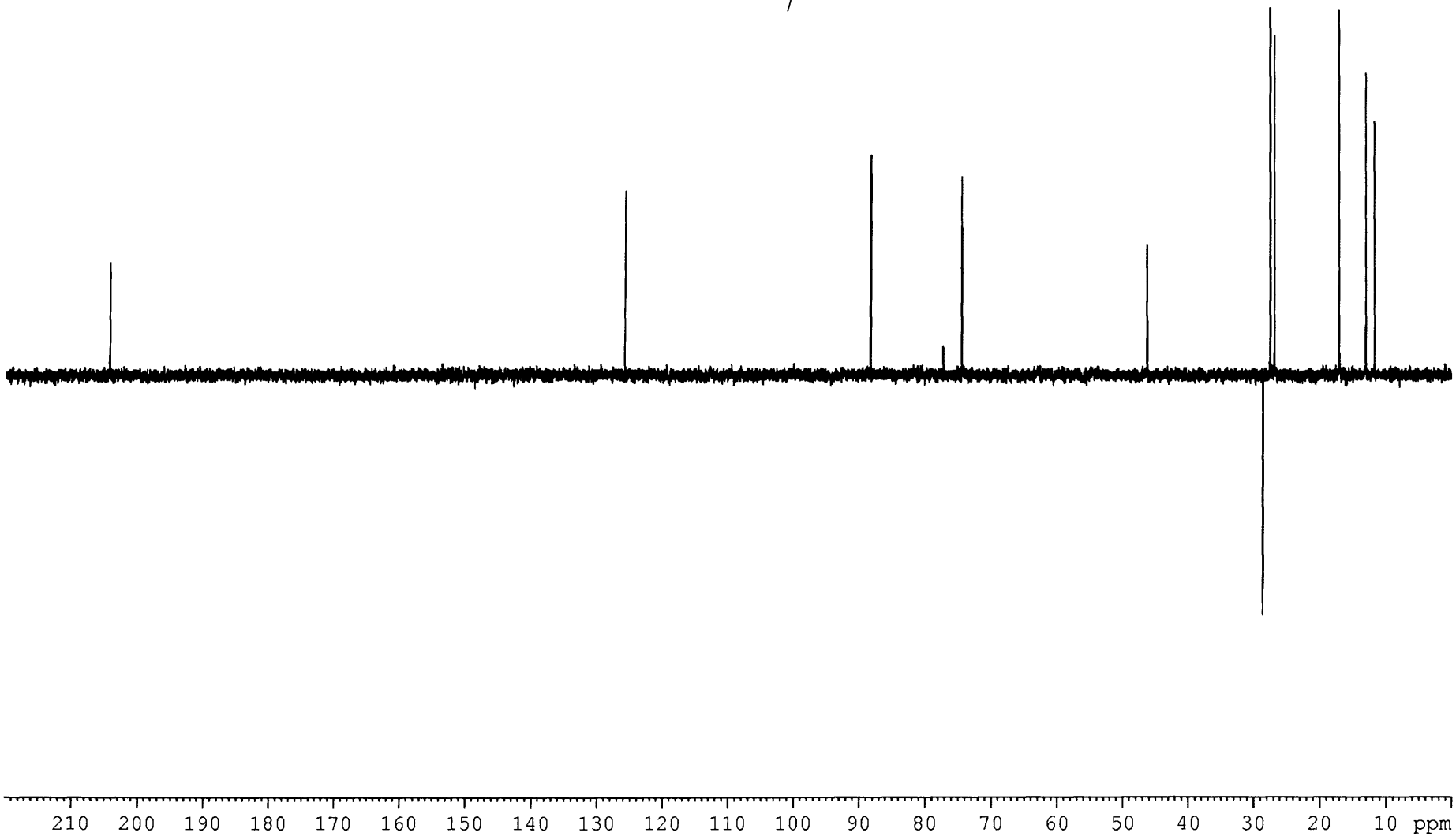

105.0
%T
100.0
95.0
90.0
85.0
80.0
75.0
70.0
65.0
60.0
55.0
50.0
3433.1
2979.8
2927.7
2877.6
1726.2
1454.2
1377.1
1238.2
1174.6
1095.5
1033.8
862.1
Me
Me
Me
HO
O
O
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0

IV-AL-173
CDCl3 - 298K

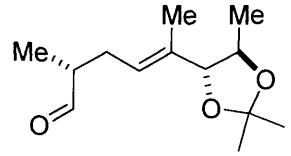


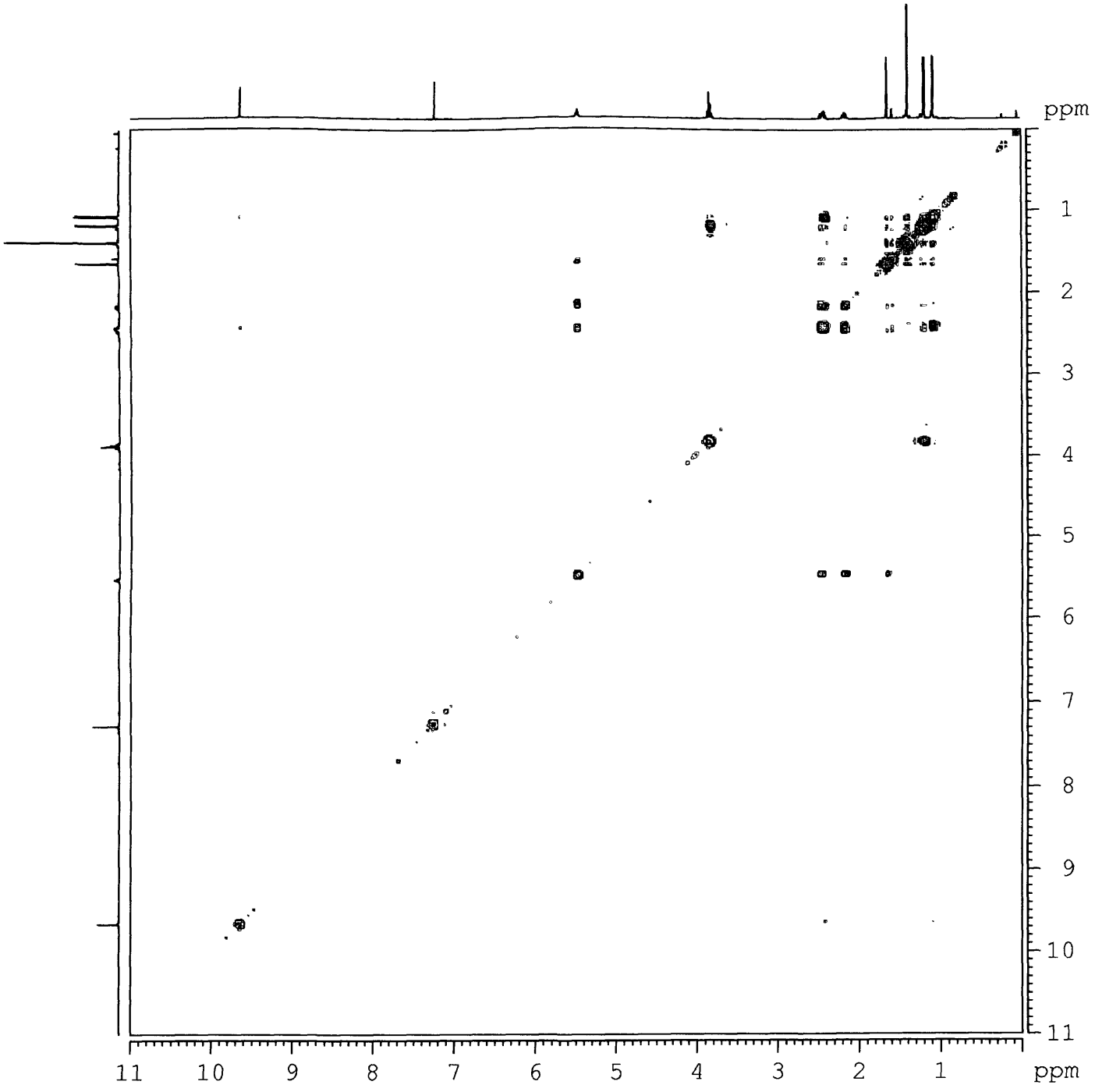
IV-AL-173
DEPT
CDCl3 - 298K



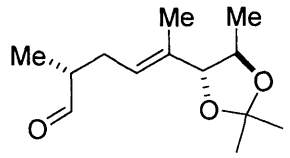


IV-AL-173
13C
CDCl3 - 298K

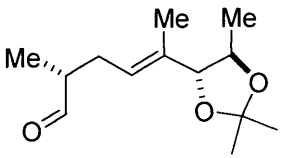


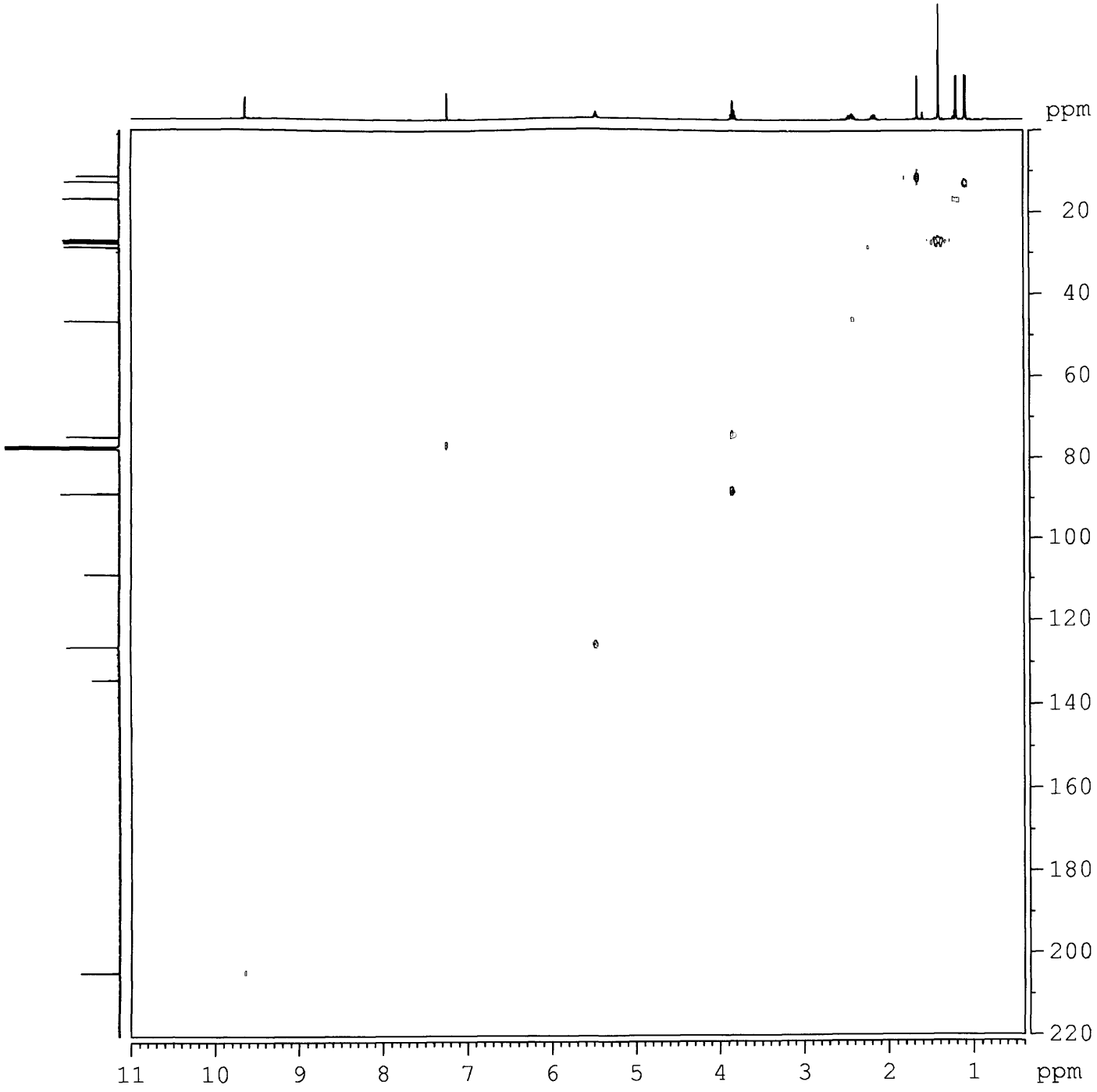


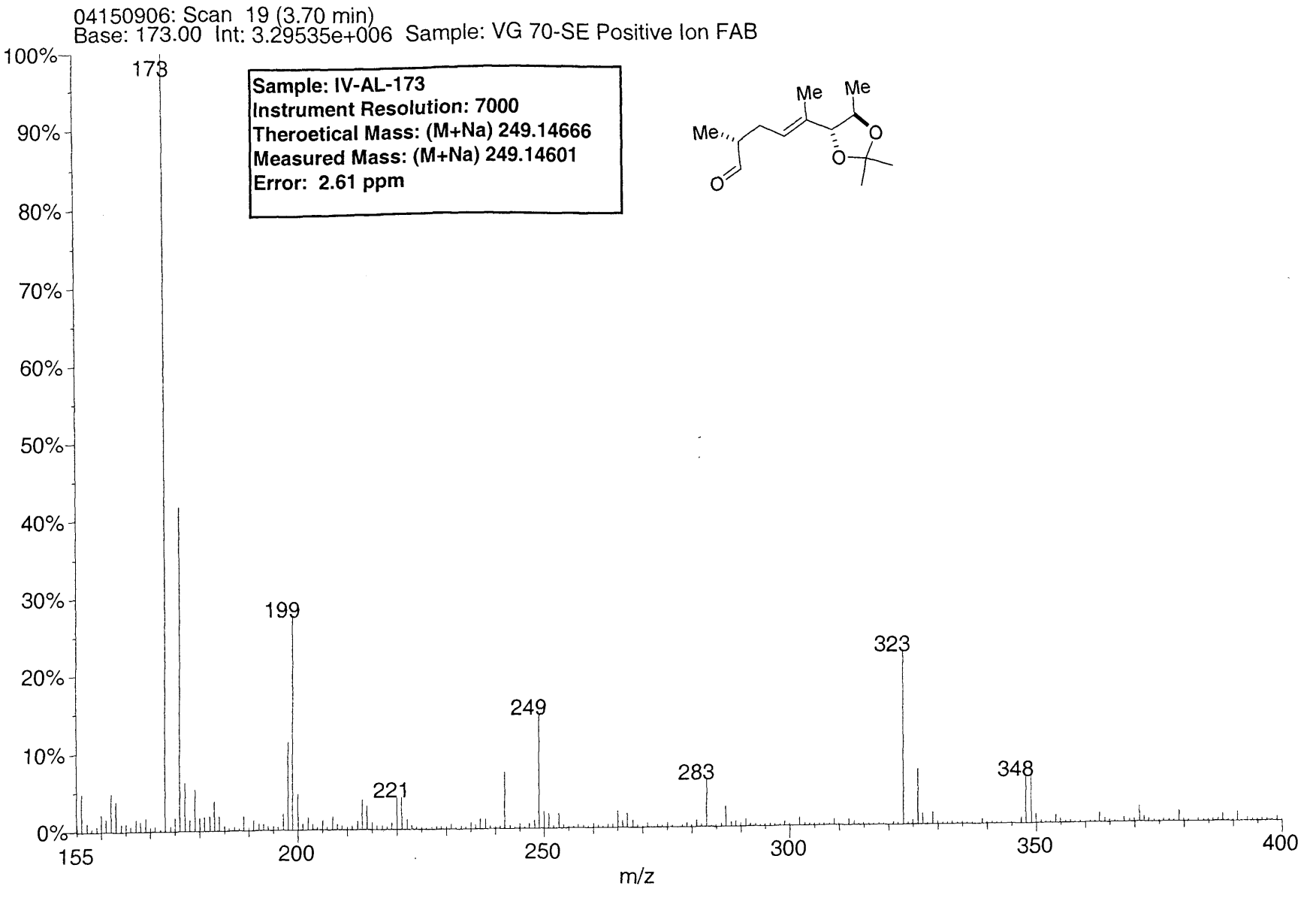
IV-AL-173
COSY
CDCl3 - 298K



IV-AL-173
HMQC
CDC13 - 298K






04150906: Scan 19 (3.70 min)
Base: 173.00 Int: 3.29535e+006 Sample: VG 70-SE Positive Ion FAB
Sample: IV-AL-173
Instrument Resolution: 7000
Theroetical Mass: (M+Na) 249.14666
Measured Mass: (M+Na) 249.14601
Error: 2.61 ppm
Me
Me
Me
O
O
O
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
173
199
221
249
283
323
348
155
200
250
300
350
400
m/z